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EDITORIAL

Is lithium potentially a trace element?

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Abstract

Lithium, a naturally occurring element, is widely used in clinical settings for psychiatric treatment. Several studies showed that micro-dose lithium (*e.g.*, lithium in drinking water) could have anti-aging and anti-dementia effects in addition to an anti-suicidal effect, although anti-mania and psychosis or anti-cancer effects are yet to be determined. Although these studies do not provide conclusive evidence, further studies are warranted to investigate whether lithium is trace element. If so, future studies would need to determine what levels are required to maintain mental health.

Key words: Lithium; Trace element; Suicide; Micro-dose; Aging; Dementia

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Core tip: Micro-dose lithium (*e.g.*, lithium in drinking water) could have anti-aging and anti-dementia effects as well as anti-suicidal effect.

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INTRODUCTION

Lithium, a natural element, is widely used in clinical settings for psychiatric treatment. On the other hand, lithium is taken up by all plants, although it appears not to be required for their growth and development. At high levels in the soil, lithium is toxic to all plants, causing a chlorosis-like condition. Uptake and sensitivity to lithium are species dependent. Consequently, grains and vegetables have 0.5-3.4 mg/kg of lithium, dairy products have 0.5 mg/kg of lithium and meat has 0.012 mg/kg[1]. Although there has been a study showing effects of nutritional lithium supplementation on mood[2], no study could directly investigate the association between lithium in the food and mental health. As already pointed out by Schrauzer[1], I wonder whether lithium is one of the trace elements or not. Generally, trace elements are dietary minerals that are needed in very minute quantities for the proper growth, development, and physiology of an organism[3]. If lithium is a trace element, various effects may be found at a very low level of lithium concentration?

TRACE LITHIUM EFFECT ON SUICIDE

With regard to very low lithium levels, there is growing

evidence from epidemiological studies that lithium in drinking water may protect against suicide. An inverse association between lithium levels in drinking water and suicide rates was first reported in the United States for 27 Texas counties[4]. In Japan, we showed an inverse association between lithium levels in drinking water and suicide rates for 18 municipalities of Oita prefecture[5] whereas another study found no association for 47 subdivisions in the East of England[6]. A nationwide Austrian study, however, found an inverse association between lithium levels in drinking water and suicide rates after adjustment for population density, per capita income, proportion of Roman Catholics, as well as the availability of mental health service providers[7].

From 2010 to 2013, we investigated the association in 274 municipalities of Kyushu Island in Japan[8]. The association of lithium levels in drinking water with suicide Standardized Mortality Ratios (SMRs) (total, male and female) were investigated thoroughly adjusting for proportion of elderly people, proportion of one person households, proportion of people with college education or more, and proportion of engaging in primary industry, overall unemployment rate, annual marriage rate, annual mean temperature and annual postal savings per person. As a result, lithium levels in drinking water were significantly and inversely associated with male suicide SMRs but not total or female SMRs after the adjustment. The findings suggest that lithium in drinking water may be associated with low risk of male but not female suicide in the general population[8]. With regard to gender differences, anti-aggressive effects of lithium could potentially prevent suicide in those who take lithium-contained drinking water for a long time and, if male aggression is greater and more responsive to lithium than female aggression, this could explain the gender effect[8]. In any case, such findings support the idea that lithium is a trace element.

With regard to the mechanism, taking the fact into consideration that lithium has been reported to increase the volume of the prefrontal cortex and anterior cingulate gyrus[9] it seems likely that lithium may at least partially exert its antisuicidal effect *via* reinforcing "top-down brakes" of aggressive action. Since lithium has been shown to increase the volume and function of the limbic system, such as the hippocampus[10], antisuicidal effects of lithium may consist of both reinforcing "top-down brakes" and decreasing "bottom-up drive." Therefore, lithium may have superior antisuicidal effects relative to other mood stabilizers[11,12].

TRACE LITHIUM EFFECT ON MANIA AND PSYCHOSIS

To our knowledge, there has been no reports on effects of lithium as a trace element on mania. This is probably because in a routine psychiatric setting we prescribe about 600-1000 mg per day of lithium to our patients for producing approximately 0.4-1.0 mEq/L of therapeutic lithium levels for mania, which is much larger than the lithium levels of drinking water.

Nonetheless, there has been a study showing that the incidence of patient's first admissions and prevalence of readmission as well as the diagnosis of psychosis, neurosis, and personality disorder to state mental hospitals from each Texas counties was inversely proportional to the lithium content of their residential drinking water[13]. At the moment, trace lithium effect on mania and psychosis is yet to be determined.

TRACE LITHIUM EFFECT ON AGING

Interestingly, an inverse correlation was found between lithium levels in drinking water and not only suicide but also all-cause mortality in 18 neighboring Japanese municipalities with a total of 1206174 individuals[14]. Taken together with another finding that an exposure to a comparably low concentrations of lithium chloride extended the life span of Caenorhabditis Elegans, these findings suggest that long-term low-dose exposure to lithium may exert anti-aging capabilities[14].

TRACE LITHIUM EFFECT ON DEMENTIA

Micro-dose lithium may also have efficacy in preventing cognitive loss. For example, 113 patients with Alzheimer's disease were randomized to receive lithium (300 μg/d) (n = 58) or placebo (n = 55) in a 15-mo, randomized, placebo-controlled, double-blind trial[15]. The lithium group showed no decline in performance on the mini-mental state examination test in contrast to the lower scores observed for placebo group, with significant differences starting 3 mo after the beginning of the treatment, and increasing progressively[15].

TRACE LITHIUM EFFECT ON CANCER

Although experimental anti-cancer effects of lithium have been shown[16], the range of lithium levels used in the study was 10 mmol/L to 60 mmol/L, which is clearly in the toxic level. Therefore, toxic effects of lithium might have brought about apoptosis in colon cancer cell line. Actually, enhanced but not reduced cancer risk was shown in bipolar disorder patients who were probably receiving long-term lithium treatment[17]. At the moment, anti-cancer effects of lithium is yet to be determined.

CONCLUSION

These findings suggest that micro-dose lithium (*e.g.,* lithium in drinking water) could have anti-aging and anti-dementia effects in addition to an anti-suicidal effect, although anti-mania and psychosis or anti-cancer effects are yet to be determined. Although

these studies do not provide conclusive evidence, further studies are warranted to investigate whether lithium is trace element. If so, future studies would need to determine what levels are required to maintain mental health. Moreover, although it seems probable that such low levels of lithium in drinking water are far below the levels required to produce aversive and side effects, it is also important to assess side-effects of lithium in drinking water on thyroid function, pregnant women, the unborn, and other potent impairment.

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REVIEW

Culturally sanctioned suicide: Euthanasia, seppuku, and terrorist martyrdom

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Abstract

Suicide is one of the greatest concerns in psychiatric practice, with considerable efforts devoted to prevention. The psychiatric view of suicide tends to equate it with depression or other forms of mental illness. However, some forms of suicide occur independently of mental illness and within a framework of cultural sanctioning such that they aren't regarded as suicide at all. Despite persistent taboos against suicide, euthanasia and physician-assisted suicide in the context of terminal illness is increasingly accepted as a way to preserve autonomy and dignity in the West. Seppuku, the ancient samurai ritual of suicide by self-stabbing, was long considered an honorable act of self-resolve such that despite the removal of cultural sanctioning, the rate of suicide in Japan remains high with suicide masquerading as seppuku still carried out both there and abroad. Suicide as an act of murder and terrorism is a practice currently popular with Islamic militants who regard it as martyrdom in the context of war. The absence of mental illness and the presence of cultural sanctioning do not mean that suicide should not be prevented. Culturally sanctioned suicide must be understood in terms of the specific motivations that underlie the choice of death over life. Efforts to prevent culturally sanctioned suicide must focus on alternatives to achieve similar ends and must ultimately be implemented within cultures to remove the sanctioning of self-destructive acts.

Key words: Suicide; Euthanasia; Martyrdom; Physician-assisted suicide; Seppuku; Hara-kiri; Terrorism; Culture

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Core tip: Although most cultures have taboos against suicide, some acts of suicide find moral justification and approval in different cultural settings. These acts typically occur independent of mental illness and are regarded as something other than suicide *per se*. Strategies for prevention therefore require the development of other culturally sanctioned alternatives.

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INTRDUCTION

For psychiatrists, suicide represents one of the few true clinical emergencies, a major public health concern, and the most frequent cause of malpractice lawsuits[1]. As a result, most of the attention to suicide within psychiatry has been devoted to prediction (identifying risk factors and developing risk assessment tools), prevention (establishing and implementing clinical practices and healthcare policies to reduce suicide rates), and forensic issues (avoiding lawsuits).

The preeminent suicidologist Edwin Shneidman conceptualized suicide as an act caused by psychological pain ("psychache") stemming from thwarted psychological needs such as love, control, shame, grief, and anger[2]. In his view, the transition from mere suicidal ideation to suicidal act is largely determined by the degree to which an individual feels that pain ("perturbation") and the degree to which one views suicide as a means to end it ("lethality"). It has been estimated that 90% of suicides are associated with mental illness, with 60% associated specifically with mood disorders[3]. Indeed, modern views on suicide in psychiatry have emphasized that "most important contributing factors to suicidal behaviors are depression, depression, [and] depression"[4].

In contrast to this psychocentric view that suicide is an act of internal despair carried out by someone who no longer finds life livable, the 19th Century sociologist Emile Durkheim proposed that suicide is determined by one's relationship to culture and society[5]. He theorized that social integration was primarily a protective force whereby excessive individuation at the expense of society increased suicide risk. But he also proposed that excessive social integration at the expensive of the individual could be just as lethal, as illustrated by examples of "altruistic suicide" in which suicide was completed as a purposeful act of social obligation, achieving some greater good to the group, or reaching the afterlife[6].

Although Durkheim's views on suicide failed to recognize individual factors and the important contribution of mental illness, examining the role of culture may be particularly useful in understanding suicide in non-clinical settings where severe mental illness is absent[7]. While Durkheim described altruistic suicide in "primitive" and "crude" cultures, such a narrow view is out of place in an increasingly globalized world. Even within cultures where there is a taboo against suicide, minority subcultural perspectives may exist that sanction such behavior. The term "rational suicide" has gained traction in recent years as a way of disentangling automatic associations between suicide, psychiatric disorder, and irrational thinking, and instead shining a spotlight on cultural sanctioned forms of suicide[1,8]. "Ruling out" mental illness when evaluating patients with suicidal ideation requires that a clinician be familiar with such practices.

This paper aims to provide a survey of culturally sanctioned suicide across the globe and over time. The overview is not meant to be exhaustive by any means and will instead focus on three key examples of suicide that have emerged within a cultural framework and should help to inform discussions of suicide in both clinical and non-clinical settings.

DEATH WITH DIGNITY: EUTHANASIA AND PHYSICIAN-ASSISTED SUICIDE IN THE WEST

In the Western world, although the concept of culturally sanctioned suicide as a means of avoiding the suffering associated with severe or terminal medical disease dates back to at least the ancient Greeks[9,10], the subsequent rise of Judeo-Christian teachings led to a longstanding and pervasive ethical proscription against suicide under almost any terms. The equation of suicide with sin even found formal translation into modern law, such that suicide was illegal in England until the 1960s and it technically remains a felony in some states within the United States today[11].

Over the past 50 years however, medical advances that now permit the extension of life in conditions previously associated with an untimely demise have resulted in growing concerns about the prolongation of suffering, loss of autonomy, and erosion of the concept of a "good" or "natural" death[12,13]. As a result, suicide in the context of intractable medical illness has gained increasing mainstream acceptance.

Limited information is available about unassisted or solo suicide in the context of suffering related to medical illness. It has been estimated that medical illness is present in up to 40% of suicides and that certain medical conditions such as acquired immunodeficiency syndrome, multiple sclerosis, and some cancers are particularly over-represented[14]. However, the specific contribution of medical illness towards suicide remains unclear owing to the considerable comorbidity of depression among such conditions and the fact that chronic medical illness is common among older people who are at greatest risk of suicide. In other words, while the presence of medical illness a well-known risk factor for suicide, a causal relationship isn't well established. In fact, the proportion of suicide victims who specifically suffer from terminal illness at the time of death appears to be quite small, in the 2%-4% range[14,15]. Other data suggest that independent of those with depression, the vast majority of those with terminal illnesses such as cancer do not wish to die[12,16-18].

In contrast to solo suicide, euthanasia, literally meaning "good death," has become something of an umbrella term for taking measures to end the life of someone with unbearable suffering associated with intractable or terminal illness. Such hastening of death is typically overseen if actually not carried out by physicians in the larger context of medical care where a spectrum of voluntary interventions is available.

These include voluntary refusal of food and liquids, withholding "heroic measures" and life-sustaining treatments such as cardiac resuscitation or intubation, palliative sedation, passive voluntary euthanasia or physician assisted suicide (PAS), and active voluntary euthanasia (AVE).

Active voluntary euthanasia refers to having a second party to actively fulfill a dying person's request to be put to death, a practice put into the spotlight by United States physician Jack Kevorkian in the 1990s. Kevorkian was ultimately tried and convicted for second-degree murder since such practice was and still is illegal in the United States. Alternatively, passive voluntary euthanasia in the form of PAS, in which a doctor provides the means (*e.g.*, lethal medication) for patients with terminal medical illness who wish to die but does not administer it, has been legalized in Oregon, Washington, Vermont, and New Mexico, while in Montana the practice has been recognized by state courts as not illegal. Outside of the United States, some form of euthanasia is legal in Belgium, the Netherlands, Luxembourg, and Switzerland. The specific circumstances that permit euthanasia vary within different states and countries. As noted, only PAS is legal in the United States, whereas in Belgium, AVE is the only legal form of euthanasia. Switzerland allows for passive voluntary euthanasia by both physicians and non-physicians. Perhaps because of the option to have euthanasia outside of medical care, Switzerland has become a popular destination for "suicide tourism", attracting those with medical illnesses who wish to die from neighboring countries in Europe where PAS is outlawed. An estimated 200 such "suicide tourists" come to Switzerland each year with the intention of ending their lives, a practice that appears to be growing[19]. In the United States and Europe where it is legal, some 0.1% to 2.9% of all deaths occur by PAS[20].

The legalization of PAS in select locales within Western countries has resulted from the active efforts of various grass roots organizations belonging to the larger "euthanasia movement" that started in the 1930s and has since come to be called the "right to die" or, more recently, the "death with dignity" movement[13,21]. As these names suggest, the primacy of autonomy, self-determination, and the right to a "good death" over the endurance of unbearable suffering lies at the core of this form of culturally sanctioned suicide. Although the term "unbearable suffering" defies objective definition, studies of people seeking PAS indicate that concerns about loss of dignity and quality of life, becoming dependent or a burden on others, intolerable pain or fatigue, loneliness, and loss of identity are the most common motivating factors[21,22].

In its purest form, the ethical justification for PAS hinges on the presence of a terminal illness and it is on this basis that some would distinguish euthanasia from suicide[9]. However, death is an inevitability for all and it isn't always clear when an illness becomes terminal. It has been argued that the growing acceptance of PAS in countries like the United States is a result of a "technological imperative"[13] in which physicians are expected to employ "any and all resuscitative measures… to prolong the life of all patients regardless of age, illness, or prognosis"[23]. In contrast, there may be less support for PAS in countries with limited healthcare resources and where life expectancy is more modest.

In addition to autonomy surrounding the right to die with dignity, religious beliefs figure heavily into one's acceptance of PAS. This is unsurprising since many religions such as Islam, Judaism, and Catholicism expressly forbid suicide and euthanasia. As a result, many people believe that "only God should decide the time of death"[22]. An international survey found that by religious affiliation, Muslims tend to be the most strongly opposed to euthanasia, followed sequentially by Catholics, Protestants, and those with no affiliation[24]. In addition, religiosity itself, irrespective of denomination, appears to be a strong predictor of opposition to PAS[18,24].

Opposition to PAS is also predicted by concerns about the "slippery slope" of legalization in which, once approved, laws concerning euthanasia might become increasingly lax. Indeed, while United States laws permitting PAS require the involvement of a physician and that the patient requesting it be mentally competent and have a terminal medical illness, several different arguments have questioned such restrictions. For example, does illness and suffering only apply to medical conditions or should it be extended to those with mental illness[25]? Should PAS be unavailable to those who have unbearable suffering from terminal illness, but lack decisional capacity? Indeed, European laws have loosened these very limitations in recent years. In the Netherlands, those with mental disorders are now eligible for PAS, while in both the Netherlands and more recently Belgium, PAS is available to those who are mentally incompetent, including children. Such developments challenge the notion of voluntariness in PAS and raise concerns about potential conflicts of interest when decisions are made by proxy. For example, could the legalization of PAS result in pressure on individuals who are burdens, financially or otherwise, on their families? In 2009, proposed legislation providing nationalized healthcare in the United States that would have allowed insurance reimbursement for physicians discussing end-of-life care with patients sparked politically-motivated claims about the anticipated formation of "death panels" that might opt to euthanize people rather than pay for medical care.

Needless to say, PAS remains a controversial and debated ethical issue throughout the world, even in places where it has been legalized. Still, acceptance of PAS has become mainstream in Westernized nations. A recent Gallup poll indicated that the majority of the

United States population believes that both AVE (70%) and PAS (51%) "should be allowed"[26]. This is striking, in that euthanasia by the hand of a physician is more accepted than PAS in the United States, despite the fact that it is AVE that is illegal. There are at least two likely explanations for this apparent paradox. The first concerns the wording of the survey, which described the AVE option as allowing doctors to "end the patient's life by some painless means" and PAS as allowing a doctor to "assist the patient in committing suicide". Given that choice, death by "some painless means" probably sounds better than "committing suicide", which conflicts with a persistent taboo against suicide in the United States. Indeed, the same Gallup poll found that nearly half the sample (49%) deemed PAS to be "morally wrong" and two-thirds of the sample (77%) stated that suicide was morally wrong[27]. Second, the greater acceptance of AVE in comparison to PAS may reflect a preference for the medicalization of euthanasia that places the direct responsibility of hastening death into the hands of physicians. The more active role of the physician in AVE may be more aligned with the range of accepted medical practices that are already in place such as palliative sedation (*e.g.*, administering a medication for pain, but knowing that it will likely hasten death – the so-called "double-effect").

There is irony in the fact that technological advances in medical care that have resulted in increased life expectancy have in turn led to greater acceptance of suicide that is specifically facilitated by physicians, particularly since the Hippocratic Oath forbids it. Not surprisingly, in contrast to the general population, United States physicians tend to have significantly greater acceptance of PAS compared to AVE[28]. There is also a discrepancy in that while many United States physicians support the legalization of PAS, a much lower proportion would agree to actually perform it[28]. Physicians in the United Kingdom have been found to support PAS at a lower rate than does the general public[29]. A study from Israel found that psychiatrists tended to oppose PAS more than other physicians, but there may have been unique cultural factors pertinent to their sample[30]. Palliative care specialists appear to have the lowest rates of PAS acceptance[31] and physicians' knowledge about palliative care is inversely correlated with PAS acceptance[32]. This suggests that support for PAS may be based on a lack of knowledge about other options such as palliative sedation or hospice care.

As with the rest of the population, the religious beliefs of healthcare workers also contribute significantly to their attitudes regarding PAS[22,29-33]. However, it is also likely that while ending the life of someone suffering from a terminal illness is becoming increasingly culturally sanctioned, both physicians and non-physicians must still struggle with cultural taboos against suicide and murder such that their attitudes about PAS and AVE are heavily influenced by imagining their own part in it. In the United States, the general public seems to prefer that physicians perform the deed, whereas physicians prefer that patients do it. In short, when considering an abstract scenario involving euthanasia, most are reluctant to "get their hands dirty".

For those actually struggling with terminal illness however, the distinction between AVE and PAS appears to be less important. A study of cancer patients receiving palliative care in Canada found that the majority favored the legalization of either PAS (56.5%) or AVE (59.1%), although only 5.8% would request it right away if available[17]. While still controversial and subject to different legal details depending on locale, some form of euthanasia is an increasingly culturally sanctioned option of self-determination for those who prefer suicide over continued suffering from terminal illness.

DEATH WITH HONOR: SEPPUKU IN JAPAN

From a historical standpoint, there is probably no more iconic form of culturally sanctioned suicide than the Japanese tradition of seppuku. The terms seppuku ("cutting the stomach") and hara-kiri ("belly cut") both refer to the ancient rite of stabbing the lower abdomen and disemboweling oneself with a short sword. Death typically ensued not from the stomach wounds, but rather by the swift strike of a kaishakunin, or second, who stood at the ready with a long sword to behead the person performing seppuku. Seppuku was a highly ritualized exercise limited to the Japanese warrior caste, the samurai, with its sanctioned practice spanning from the 700s until it was formally outlawed in 1873[34,35].

In its most idealized form, seppuku was an act that, at its heart, symbolized resolution in the face of death. For the samurai class, "the meaning of life was understood in terms of one's ability to find the right time and place to die"[36]. In *Hagakure* ("Hidden Leaves"), a sort of manual for samurai behavior, the author writes, "the Way of the Samurai is found in death. When it comes to either/or, there is only the quick choice of death… Meditation on death should be performed daily… every day without fail one should consider himself dead"[37]. A similar text, *Budoshoshinshu*, notes, "The man who would be a warrior considers it his most basic intention to keep death always in his mind… Day and night without fail, as one is involved in all his business, both public and private, when there is just a moment for the heart to be calm, death should be kept in mind"[38].

To place such value on the readiness for death is understandable for a class of warrior elite, whose chief aim was to serve a lord in wartime (the literal meaning of samurai is "to serve nobility"). For a samurai, death in battle was regarded as among the highest honors. Accordingly, the act of seppuku was typically performed by samurai as an honorable "out" in lieu of surrendering to the enemy, to make amends for

personal failings, or in following one's lord to the grave. Rather than being nihilistic or death-hungry, to embrace suicide in this way was viewed as affirming a life rooted in ideals of loyalty, duty, honor, and self-sacrifice, as reflected by the term for voluntary seppuku, jiketsu ("self-determination")[36,39]. Still, while seppuku was regarded as an honorable act, it was often performed in the context of avoiding dishonor. Any apparent contradiction finds potential resolution in the teachings of Zen Buddhism, which became deeply entwined with the study of swordsmanship during the samurai era. With the constant threat of death, Zen's emphasis on impermanence, the illusory nature of the self, and detachment from dualistic ideas about life and death seem to have had special appeal to the samurai[36,40-42]. At a very basic level, the study of Zen, which holds not proscription against suicide[43] as well as no promise of an afterlife, helped the samurai to gain mastery over the fear of death[42]. Seppuku, it could be argued, was emblematic of that mastery. Indeed, tales of completed seppuku describe steadfast preparation for the act; extended, criss-crossed cuts to the abdomen performed without unsightly emotional displays; and even claims of reaching into the resulting wound to extract one's intestines which were then defiantly flung to the ground[34].

Although such accounts have been romanticized throughout Japanese history to the present day as embodying the essence of bushido (the "way of the warrior"), several authors have called into question the very existence of any such samurai code beyond an often unrealized ideal akin to chivalry[44,45]. In fact, the reverence of death readiness described in *Hagakure* and *Budoshinshu* occurred during a period of prolonged peacetime following the unification of rival warlords and therefore represented a kind of harkening back to, or yearning for, a lost era. In actual practice, seppuku was not always limited to the narrow confines of a valorous samurai ritual, but also occurred in the context of all manner of motivations including "shame, desperation, grief, panic, protest, patriotism, narcissism, revenge, hatred, and love"[34], not to mention depression and murder. By the 1600s, the purpose of seppuku was extended to a form of involuntary capital punishment rather than a self-initiated act and by the 1700s, voluntary self-stabbing was often relegated to a symbolic gesture, with a paper fan replacing the sword and death coming instead by timely decapitation[34-36]. In this sense, seppuku has been described as an "elaborate aesthetic framework that has been constructed around [a] skeleton of truth… augmented by myth and adorned with aesthetic trimmings"[34].

Nonetheless, despite the abolishment of the samurai class, the prohibition of carrying swords, and the outlawing of seppuku in the 1870s as Japan adopted a Westernized form of government and military, seppuku has continued to be viewed as an act of courage, honor, and self-sacrifice within modern Japanese culture. One of the best-known and beloved tales in Japanese history is the Chūshingura, or fictionalized retelling of the true-life exploits of a group of masterless samurai, the 47 ronin, who committed seppuku after avenging the death of their lord in the early 1700s. In the past century, samurai ideals and the idea of seppuku along with it have been revived during periods of patriotic nationalism, most prominently during World War Ⅱ. During that era, Japanese soldiers equipped with both modern firearms and mass-produced swords committed seppuku rather than surrender to enemy forces. The spirit of seppuku, if not the technical practice, was likewise epitomized by the so-called kamikaze bombers who, facing defeat at the end of the war, deliberately piloted their airplanes into enemy vessels. In 1945, both soldiers and civilians alike committed seppuku in droves as an apology for having lost the war[35]. More recently, in 1970, the celebrated author Yukio Mishima committed seppuku in an act of political protest seemingly intended to inspire a return to nationalism. Though other motivations have been proposed[45-48], Mishima clearly revered samurai ideals in his work, was himself well-versed in Japanese swordsmanship, and had written specifically about the honor of seppuku in a short story called "Patriotism"[49].

In modern Japan, there is little remaining cultural framework for seppuku, such that suicide by stabbing the abdomen has become extremely infrequent, comprising only 0.2%-4.5% of all suicides[35,50]. But suicide in general has remained something of a culturally sanctioned act, depending on context. Since 1998, the suicide rate in Japan has been elevated at nearly 25 per 100000 people with over 30000 suicides per year[51], such that Japan has been called a "suicide nation"[52]. As the martial philosophies of the samurai era have been adapted to the business world, newer modes of suicide have emerged. Two such forms that have received recent attention are inseki jisatsu, or "responsibility-driven suicide," and karo jisatsu, or "suicide by overwork." These forms of suicide refer to motivation rather than methodology. Inseki jisatsu is a form of suicide that represents taking responsibility for a personal failing, as in the case of a school principal who committed suicide after a student was killed in an accident on school grounds[53]. Karo jisatsu refers to suicide that occurs in the context of excessive overwork and is typically accompanied by burn-out and depression[54]. Among young people in Japan, suicide by charcoal burning (resulting in carbon monoxide poisoning) reached epidemic proportions starting in 2003[55], as has the phenomenon of internet suicide pacts[52]. Of these modes of modern suicide, inseki jisatsu most resembles the spirit of seppuku, with completers often earning posthumous praise and reverence in the eye of the public. For example, when Yoshikatsu Matusoka, the Minister of Agriculture, Forestry, and Fisheries hung himself under a cloud of suspicion about inappropriate use of public funds in 2007, he was called a "true samurai" by the governor

of Tokyo. Karo jisatsu has come to be modeled as a kind of industrial accident, such that completers are often viewed as victims of an overly demanding Japanese work ethic and other social pressures rather than individual issues of mental health[56]. Suicide in Japan is associated with long work hours and is negatively correlated with income and time spent in leisure activities[57]. As a result, the increasing recognition of karo jisatsu has created potential liability for employers and has prompted workplace reform. In contrast, participants in shinjyu, or "suicide pacts", lacking the purposeful motives of seppuku dictating an honorable death, most conform with a model of suicide as reflecting mental illness and the absence of ikagai, or "worth of living". Participants are therefore often viewed with derision as "copycats or too weak-willed to die alone"[52].

The medical literature includes a number of case reports and retrospective studies from Japan describing suicide or suicide attempts by stabbing or cutting the abdomen. Based on these reports, suicide attempts and completed suicide by cutting the abdomen is typically performed with a kitchen knife[58,59] as opposed to a "samurai sword", with numerous preliminary "hesitation cuts" indicative of self-stabbing[35,60,61]. Overwhelmingly, this method of self-injury is performed by men rather than women, with mental illness found in the majority of cases[35,50,58-62]. The frequent presence of mental illness, usually in the form of mood or psychotic disorders, suggests that these acts were something altogether different than ritual seppuku, despite the fact that about half of these reports explicitly use the literal term "hara-kiri" in describing the abdominal cuts. Although Takai and colleagues[50] refer to a potential "change [in] the meaning of hara-kiri", it would be more correct from a motivational standpoint to avoid the terms hara-kiri or seppuku in such cases. Just because a suicide by stabbing the abdomen occurs in Japan does not make it seppuku.

This mistake in terminology is even more notable among the handful of cases of so-called hara-kiri and seppuki reported in non-Japanese countries. These cases, occurring in the United States[63], Australia[64], Italy[65], and Ireland[66], again document the presence of depression, psychosis, substance abuse, or personality disorder in almost all instances. Another recent report described a case of jigai, or ritual stabbing of the neck, historically performed by samurai women in a corollary ritual to seppuku[67]. However, although the completed suicide was performed in a bathtub with a replica samurai sword, the perpetrator was not a woman, but rather a man with a history of "long-term depression." While such cases suggest that the acts have been inspired by the Japanese tradition of seppuku, the absence of any such cultural sanctioning in other countries and the omnipresence of mental illness suggest that they should be described simply as suicide or suicide attempts by self-stabbing[68] rather than seppuku, hara-kiri, or jigai. Indeed, it has been argued that equating mere acts of self-stabbing with seppuku is "misleading at best, just as a casual benediction offered among friends while serving wine and crackers as refreshments ought not to be equated with the rite of Catholic Eucharist"[69].

Suffice it to say that over time, the cultural sanctioning of suicide in Japan has evolved from the mythologized ideal of seppuku into something altogether distinct. Seppuku as performed by the samurai class was an aesthetic and social ritual that imparted posthumous heroism into the completer with preservation of honor for his bloodline. Although we cannot know the true rate of mental illness among such acts, seppuku does not appear to have been the act of someone with mental illness except in rare cases of "plain suicide"[34]. Today, the high rate of suicide among the general population of Japan suggests that suicide under the right circumstances retains some degree of cultural sanctioning, but seppuku as a sanctioned social ritual has been phased out. Without the use of a kaishakunin, acts of self-stabbing are more often suicide attempts than completed acts. For those that attempt suicide in this fashion, loneliness and despair stemming from depression, psychosis, or the cultural bound syndrome hikikomori that is characterized by severe social withdrawal[70,71] is now the rule. Therefore, outside of inseki-jisatsu, the traditional motivation for seppuku in Japan has been all but lost. Accordingly, there been a shift away from a view of suicide as an act of individual freedom and self-determination to a more medicalized version that has only recently been imported from the West[56]. This new cultural view of suicide has led to the widespread implementation of psychoeducation, public policy prevention measures, and enhanced mental health services in Japan[51,72].

DEATH AS MARTYRDOM: SUICIDE TERRORISM IN ISLAMIC MILITANT GROUPS

Although murder-suicide has been carried out in the name of religion across a spectrum of cultures and faiths throughout history, much attention has been devoted in the psychiatric literature to suicide terrorism as a war tactic of Islamic militants since the World Trade Center attacks of September 11, 2001. The modernity of this issue has two main implications for the understanding of suicide in this context. First, unlike seppuku, what is known about suicide terrorism does not depend on a mythologized historical archetype, but is rather something that exists now and continues to evolve in real-time. Second, the timeliness of this practice in the context of active war means that the issue remains highly charged with wildly divergent cultural views, problems of cultural translation, and biases of propagandization.

A few neutral definitions are therefore in order

to start. Terrorism is an act of violence or threatened violence that intends to provoke fear. Suicide terrorism adds the intended self-inflicted death of its perpetrator. While some have specified that suicide terrorism be directed at "non-combatants"[73] or be "politically motivated"[74], those are ill-defined and debatable modifiers. As the popular saying goes, "one man's terrorist is another man's freedom fighter". Importantly, those who sanction suicide terrorism in the context of modern day Islamic militancy do not view such acts as suicide, but as shahada or istishhad (both translated as "martyrdom")[75-78]. In fact, Islam expressly forbids intihar, or suicide proper[78-80], such that militant interpretations of Islamic scripture sanction suicide terrorism as an act of shahada performed in the spirit of jihad[75,79]. Although typically translated in the Western literature as "holy war," the term jihad is literally translated as "struggle" and carries a broader meaning that implies self-defense against anything that threatens an idealized way of life according to Islam[76,77]. Such threats include generic concepts of temptation and sin, but also Jahilyyah, or barbarism, that is equated with the kind of secularism associated with life in Western countries[81]. According to this broad view of threat, those who sanction suicide terrorism believe that there are no non-combatants or innocents to speak of[82].

While this perspective is difficult to accept in the West, attempting an understanding of the motivations of suicide terrorism is necessary to see how such behavior is culturally sanctioned as opposed to emblematic of psychopathology. In fact, overall rates of suicide in Muslim countries are among the lowest, with Islamic faith seemingly having a moderating effect[79]. Looking at perpetrators of suicide terrorism, the vast majority appear to be free of mental illness[73,80,83,84]. On the contrary, it has been noted that those who recruit suicide bombers specifically avoid those with mental health issues in favor of young men with college educations and the necessary social, linguistic, and technical skills to carry out complex operations[73]. Likewise, counter to stereotypes, impoverishment is not a specific predictor of suicide terrorism. Many Palestinian suicide bombers in the late 1990s were educated, middle-class men[85] and most of the perpetrators of the World Trade Center attacks came from comfortable, middle class families[80], while a survey of the militant group al Qaeda revealed that the majority of members were college graduates from middle to upper class homes who were married and had children[76]. It has been further suggested, perhaps in the spirit of propaganda, that martyrdom or self-sacrifice for Allah would have less meaning if individuals had nothing to lose[73]. Even popular assumptions about the role of Islam itself in suicide terrorism have been called into question. Despite the use of religious rhetoric to frame terrorist acts, it has been argued that religion does not lie at the root of suicide terrorism[83] and that religious motivations per se are not predictive of who becomes a terrorist[73]. Therefore, while it is easy to dismiss suicide terrorists as "crazy" religious "fanatics", "radicals", and "extremists", such pejorative terms fall short in trying to understand the origins of suicide in this context.

In the absence of psychiatric explanations of suicide terrorism, much effort has been devoted to elucidating potential psychological factors that influence this behavior. By nature, the methodology of this research has been for the most part limited to interviews of those aspiring to suicide terrorism or of the family and friends of completed suicides. What emerges is a heterogeneous set of motivations that are often classified as related to both individual psychology and group dynamics.

Returning to the concept of martyrdom, it appears that its appeal is determined by powerful social forces[78] such as active recruitment as well as general cultural sanctioning. In Palestine today, it has been noted that young people don't aspire to be sports stars or professionals, which may be beyond their grasp in any case, but martyrs[86]. For both children and young adults alike, it is easy to see why. Martyrs are idolized as heroes, with trading cards[80], calendars, posters, graffiti, songs, and celebrations dedicated to their honor[85]. That may be little consolation in death but for the fact that martyrdom is regarded by the faithful as a pathway to an afterlife that promises a paradise replete not only with 72 virgins (as is often mentioned in the West), but an immortality in the presence and with the satisfaction of Allah[75,80]. Consequently, the final act of a martyr is said to be carried out with a bassamat al-farah, or smile of joy[84], knowing that "by pressing the detonator, you can immediately open the door to Paradise - it is the shortest path to Heaven"[85]. Beyond these individual benefits, a martyr's actions grant the ability to secure a place in paradise for 70 of his or her chosen ones, and can bestow lasting honor and material wealth unto the surviving family[75]. Collectively, these can be powerful incentives, regardless of whether an aspiring martyr comes from a life of disenfranchisement or an educated middle-class.

Ginges *et al*[87] make a compelling case for the incentives for suicide terrorism stemming from group dynamics that extend beyond self and family. Decisions to participate in suicide terrorism, they posit, are not made by conventional economic or consequentialist reasoning based on analyses of cost and benefit. This is not surprising, given that from the perspective of tangible results such as winning a war or achieving political ends, suicide terrorism is not particularly effective[88]. Instead, such decisions seem to be made using moral or deontic reasoning based on "sacred values." Deontic reasoning involves absolute rights and wrongs that trump concerns about risk or cost, leading people to act independently of outcome or prospects of success[89]. Likewise, conflicts over sacred values have the potential to result in violent behavior such as suicide terrorism. Based on experiments using subjects

in the United States, Africa, and the Middle East, Ginges *et al*[90] demonstrated that hypothetical decisions to choose militancy as opposed to diplomacy are based on sacred values that subordinate considerations about cost. Also, when exposed to political dilemmas involving perceived moral violations such as torture, subjects preferred military responses. Interestingly, using Palestinian and Israeli subjects, participants violently rejected compromise when material incentives were offered as a strategy to give up sacred values, but were willing to compromise when apologies and other symbolic gestures of respect were offered[91]. Based on neuroimaging studies, such deontic reasoning based on sacred values seems to be localizable to specific brain regions[89].

Importantly, this research on sacred values indicates that the motivations for political violence are not unique to Islamic militants. Still, it begs the question of what sacred values drive participation in suicide terrorism within this population. In addition to the religious concepts of jihad and martyrdom, the sacred values of Islamic militants may also be related to a collective identity rooted not only in religion, but geography and ethnicity. It has been shown that strong identification with a particular culture or subculture is predictive of the willingness to participate in political violence, for example, as a way to gain "justice for my people"[87].

For Islamic militants, the thirst for justice may be born out of a variety of circumstances that begin with a longstanding unrealized wish to restore the caliphate that peaked in the 600s during the "Golden Age of Islam"[76,81]. Coupled with the fall of the Ottoman Empire, the military occupation of Palestine, and the current economic success of the West, there are ample grounds for collective feelings of humiliation, resentment, and victimhood[81,92]. On a more personal level, many suicide terrorists have reported that the death of a friend or family member in war spurred them into joining the cause[76]. In this way, instrumental terrorism intended for political gain can transform into retributive terrorism, that is, terrorism for the sake of revenge[93].

As the "War on Terror" becomes, or is perceived as becoming, a "War on Islam," a growing number of people may come to identify with the sense of "us" and "them" that underlies Islamic militancy. Although suicide terrorism is extremely rare, a 2001-2007 survey of Muslims around the world found that 37% felt that the World Trade Center attacks were at least "somewhat justified"[87]. Women are increasingly participating in suicide terrorism[86] and current events suggest that a small but growing number of Muslims born in the West are "radicalizing" and traveling to the Middle East to join Islamic militant groups. These developments are understandable as Muslims around the world fueled by a growing sense of global persecution and marginalization come to identify with a "fictive kin"[73]. As one author puts it, "martyrdom operations are nothing except a declaration of refusal to live in a world of humiliation and defeat"[79]. Islamic fundamentalism, it has been noted, emphasizes not only faith, but action[81]. Based on sacred values of ideology and group identity, suicide terrorism can become a "moral imperative"[90].

The motivations for suicide terrorism discussed thus far are not meant to be comprehensive, but could nonetheless inform strategies for reducing or preventing this form of violent suicide. For example, current patterns of militant retaliation or racial profiling may only escalate violence, deepen resentments, and as is often claimed by militants, stimulate recruitment of those willing to participate in suicide terrorism[73,93]. Instead, more successful strategies might include taking care not to demonize Muslims as a whole, allying with and empowering moderate majorities, helping to build an economic infrastructure and opportunities for those who feel oppressed by circumstances, and thinking about suicide terrorism as a public health issue[74,94]. Post[80] has proposed that psychological interventions aimed at winning over "hearts and minds" is an underutilized but necessary approach to counter-terrorism efforts. This is not to say that there are simple solutions; only that understanding the motivations for suicide terrorism, and terrorism in general, is a necessary starting point. Also, if suicide terrorism is to be prevented, it is its cultural sanctioning that needs to be reversed. Therefore, alternatives must ultimately emerge from within the sanctioning culture rather than being imposed from without.

CONCLUSION

Assuming that one chooses to commit suicide, and that free will exists, the basic choice is between life and death. A psychiatric view of suicide tends to view this decision as biased by the presence of psychopathology that makes life seem worse than it is or can be. It is therefore the role of psychiatry to prevent suicide by treating mental illness. However, an alternative view is that not all suicides ought to be equated with mental illness. Rather, in some circumstances suicide may carry confer certain advantages such as autonomy, honor, or self-sacrifice that make choosing death more appealing than either life or the eventual "natural" death that awaits us all. Though the case for free will is debatable[95], these stereotypically human choices that favor an ideal or abstraction over the instinct for self-preservation would seem to represent the closest thing[96]. In contrast to suicide in the context of mental illness, these acts of ultimate self-determination are often granted an elevated status through cultural sanctioning. As a result, culturally sanctioned suicide is not typically called suicide at all, but instead becomes translated into different words such as euthanasia, seppuku, or istishhad with altogether different meanings.

For both cultural sanctioning and clinical evaluation, understanding the precise motivations behind plans

for suicide is of paramount importance. Depression may very well lurk behind apparent cases of intended or completed culturally sanctioned suicide, but so too might other psychological conflicts that do not represent mental illness *per se*. Up to 47% of patients requesting euthanasia may be suffering from depression[97] and might reverse their decision if depression, pain, or other physical discomforts were properly identified and treated. Despondent souls, whether in Japan or abroad, might cloak their suicides in the ritual trappings of seppuku in the hopes of masking an act of desperate loneliness[69]. Resentful young immigrants who find themselves displaced and unaccepted on foreign soil might seek acceptance and meaning in traveling to the lands of their fictive kin to volunteer for suicide terrorism[98], whereas those who recruit them might be purposely exploiting a vulnerable population[99]. In this regard, although cultural sanctioning can serve as an incentive for suicide, that sanctioning could very well be lost upon closer examination for underlying psychopathology or when revered motives are absent.

Analyzing suicide in terms of mental illness or not, rationality or not, and even cultural sanctioning or not is shortsighted. Just as the presence of mental illness does not automatically render suicide irrational[1,25], the absence of mental illness does not mean that suicide is the "right" decision, and the presence of cultural sanctioning does not mean that clinicians and cultures at large should not try to prevent suicide. However, cultural sanctioning is moral sanctioning, such that efforts to prevent culturally sanctioned suicide may have to be grounded in utilitarian strategies rather than moral or libertarian arguments[1]. In other words, by definition, preventing culturally sanctioned suicide based on arguments that about what is "right" and "wrong" may be futile. Instead, preventing any form of suicide, whether sanctioned or not, must focus on elucidating its particular motivations and developing appealing alternatives. When mental illness is involved, the treatment of an underlying condition is an obvious alternative. But when the motivation for suicide is an abstract cultural ideal such as honor or self-efficacy, other ways to achieve those ideals within an existing cultural framework must be explored. Thinking along these lines, palliative care and palliative sedation might be acceptable options to attain death with dignity among the terminally ill. In Japan, public health efforts directed at destigmatizing mental illness, promoting workplace reform, and encouraging leisure activity could make a healthier national lifestyle more honorable than being a suicide nation. And developing more effective ways to achieve political change, economic vitalization, and pride within a surrounding culture could remove the appeal of suicide within the violent subculture of Islamic militancy. Ultimately though, such alternatives must emerge from within a sanctioning culture - for culturally sanctioned suicide to decline, it must eventually be desanctioned.

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REVIEW

Role of perinatal long-chain omega-3 fatty acids in cortical circuit maturation: Mechanisms and implications for psychopathology

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Abstract

Accumulating translational evidence suggests that the long-chain omega-3 fatty acid docosahexaenoic acid (DHA) plays a role in the maturation and stability of cortical circuits that are impaired in different recurrent psychiatric disorders. Specifically, rodent and cell culture studies find that DHA preferentially accumulates in synaptic and growth cone membranes and promotes neurite outgrowth, dendritic spine stability, and synaptogenesis. Additional evidence suggests that DHA may play a role in microglia-mediated synaptic pruning, as well as myelin development and resilience. In non-human primates *n*-3 fatty acid insufficiency during perinatal development leads to widespread deficits in functional connectivity in adult frontal cortical networks compared to primates raised on DHA-fortified diet. Preterm delivery in non-human primates and humans is associated with early deficits in cortical DHA accrual. Human preterm birth is associated with long-standing deficits in myelin integrity and cortical circuit connectivity and increased risk for attention deficit/hyperactivity disorder (ADHD), mood, and psychotic disorders. In general, ADHD and mood and psychotic disorders initially emerge during rapid periods of cortical circuit maturation and are characterized by DHA deficits, myelin pathology, and impaired cortical circuit connectivity. Together these associations suggest that early and uncorrected deficits in fetal brain DHA accrual may represent a modifiable risk factor for cortical circuit maturation deficits in psychiatric disorders, and could therefore have significant implications for informing early intervention and prevention strategies.

Key words: Omega-3 fatty acids; Brain development; Prefrontal cortex; Docosahexaenoic acid; Connectivity; Attention deficit/hyperactivity disorder; Mood; Cognition; Bipolar disorder; Schizophrenia; Amygdala

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Core tip: Although the role of perinatal brain omega-3

fatty acid (DHA) accrual on the maturation and long-term stability of cortical circuitry is only beginning to be fully understood, extant translational evidence suggests that DHA plays a role in the initial development and early maturation of cortical circuits. Emerging evidence from human neuroimaging studies further suggests that psychiatric disorders that initially emerge in childhood and adolescence and associated with low blood DHA levels are characterized by frontal circuit deficits compared with healthy developing youth. Based on existing evidence, these associations could have significant implications for informing novel early intervention strategies aimed at reducing the transmission of psychopathology.

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INTRODUCTION

Over the past 30 years evidence has emerged from both animal and clinical research implicating long-chain omega-3 (LC*n*-3) fatty acids in normal brain development and function. The principal LC*n*-3 fatty acid found in mammalian brain gray matter is docosahexaenoic acid (DHA), which comprises approximately 10%-20% of total fatty acid composition in the adult frontal cortex[1,2]. Although the omega-3 fatty acid precursors of DHA, including α-linolenic acid (ALA, 18:3*n*-3), eicosapentaenoic acid (EPA, 20:5*n*-3), and docosapentaenoic acid (22:5*n*-3), cross the blood-brain barrier, they are rapidly oxidized and consequently comprise < 1% of total brain fatty acid composition[3]. Mammals require a dietary source of *n*-3 fatty acids to procure and maintain adequate concentrations of DHA in peripheral and central tissues. Although DHA can be biosynthesized from the vegetable short-chain *n*-3 fatty acid precursor ALA *via* a series of microsomal desaturase, elongase, and peroxisomal reactions, preformed DHA is significantly more effective than ALA for increasing erythrocyte[4], breast milk[5,6], and cortical gray matter[7,8] DHA concentrations. Primary dietary sources of DHA include cold water fatty fish, milk and eggs fortified with DHA, and fish oil (FO) or algal supplements.

Human infant, childhood, and adolescence are critical developmental periods associated with the formation and establishment of structural and functional connectivity between frontal lobe regions that mediate attention and executive function and limbic structures that mediate emotion and mood[9-11]. During this perinatal period DHA concentrations increase sharply in the frontal cortex[1] and may therefore play an important role in cortical circuit maturation. This is supported in part by recently emerging neuroimaging data that suggests that DHA status is positively correlated with frontal cortex structural and functional integrity in human subjects across the lifespan[12]. Moreover, preterm delivery is associated with early deficits in cortical DHA accrual, long-standing deficits in cortical circuit maturation, and increased risk for developing psychiatric disorders. Lastly, psychiatric disorders which frequently initially emerge during rapid periods of cortical circuit maturation and are characterized by DHA deficits, myelin pathology, and impaired cortical circuit connectivity (see below). These associations support the hypothesis that LC*n*-3 fatty acids play a role in the early development of cortical circuits and that LC*n*-3 fatty acid insufficiency may represent a modifiable neurodevelopmental risk factor for psychiatric disorders. This review critically evaluates translational evidence implicating LC*n*-3 fatty acids in cortical circuit development, highlights plausible molecular and ultrastructural mechanisms, and explores potential relevance to the pathoetiology of recurrent neuropsychiatric disorders.

RODENT NEURODEVELOPMENT

During perinatal rodent brain development, cortical DHA concentrations increase sharply in conjunction with active periods of neurogenesis, neuroblast migration, and synaptogenesis[13]. For example, there is a 5-fold increase in cortical DHA levels during the late gestation compared with early gestation[13]. DHA preferentially accumulates in neuronal growth cone[14,15] and mature synaptic[16,17] membranes where it modulates membrane signaling dynamics and synaptogenesis[18,19]. DHA also increases neurotrophic factor expression including nerve growth factor (NGF) and brain-derived growth factor (BDNF)[20,21], and promotes neurite outgrowth[22-26]. Dietary-induced deficits in brain DHA accrual during perinatal maturation are associated with reductions in neurogenesis[27,28], delays in neuronal migration and embryonic cortical plate expansion[29,30], and reduced synaptic plasticity and connectivity[24]. Additionally, DHA and its bioactive metabolites are protective against a variety of neuronal insults associated with oxidative stress and lipid peroxidation in the fetal[31-33] and adult rat brain[34-39].

One consequence of changing the fatty acid composition of cellular membranes that is relevant to synaptic maturation and function is the alteration of phospholipid composition. Specifically, perinatal deficits in DHA accrual are associated with selective reductions in neuronal membrane phosphatidylserine concentrations[40,41], whereas perinatal FO supplementation selectively increases neuronal membrane phosphatidylserine concentrations[23,42]. Importantly, phosphatidylserine modulates the activity of signal transduction proteins including protein kinase C (PKC)[43]. PKC plays a pivotal role in filamentous actin (F-actin) cytoskeletal structural plasticity required for neurite outgrowth, growth cone motility, dendritic spine formation and stability, as well

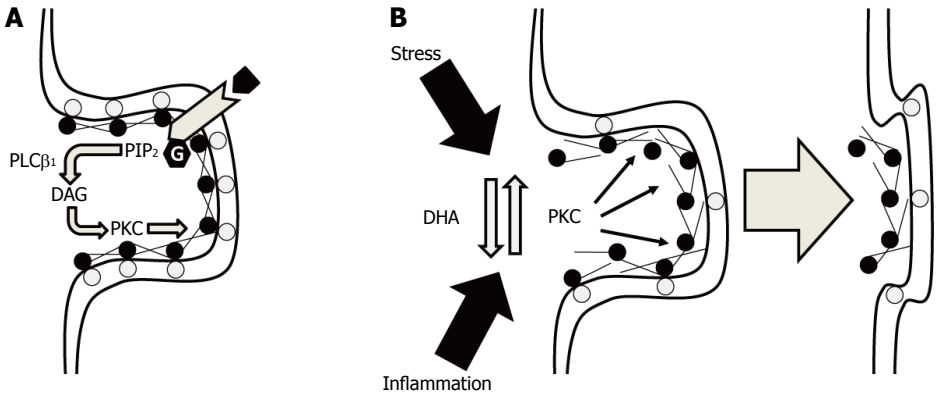

Figure 1 Potential ultrastructural mechanisms by which membrane DHA deficits could lead to a loss in synaptic connectivity. A: Under normal physiological conditions, synaptic membrane phosphatidylserine (gray circles) bind MARCKS (black circles) at the membrane which also cross-links and tethers F-actin to support dendritic spine cytoskeletal structural stability. Binding of MARCKS with membrane phosphatidylserine also inhibits phospholipase Cβ1-mediated hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP_2) into diacylglycerol (DAG) which increases PKC activity. PKC-mediated phosphorylation of MARCKS reduces the tensile strength of the F-actin cytoskeleton leading to the eventual collapse of the spine; B: Under conditions of membrane DHA deficits, reductions in membrane phosphatidylserine and membrane-bound MARCKS increase PKC activity and destabilizes the F-actin cytoskeleton leading to spine collapse. Elevated PKC activity secondary to membrane DHA deficits may also reduce the resilience of dendritic spines to other pathophysiological factors including chronic stress or inflammation. DHA: Docosahexaenoic acid; PKC: Protein kinase C; MARCKS: Myristoylated alanine-rich C kinase substrate.

as neurotransmitter release dynamics[44]. This response is mediated in part by PKC-mediated phosphorylation of substrate proteins including myristoylated alanine-rich C kinase substrate (MARCKS) which cross-links actin filaments in a phosphorylation-reversible manner[45]. Moreover, MARCKS binds membranes in part by electrostatic interactions between phosphatidylserine and the highly basic phosphorylation site domain in a phosphorylation-reversible manner[46]. Consistent with this mechanism, we demonstrated that perinatal deficits in DHA accrual were associated with a significant reduction in membrane-bound MARCKS, and an associated increase in cytosolic MARCKS, in the rat hippocampus[47]. These findings suggest that lower membrane phosphatidylserine content in response to reduced DHA levels are associated with a dysregulation in the signal transduction processes that regulate F-actin cytoskeletal structural plasticity.

Electrostatic binding of MARCKS with membrane phosphatidylserine also inhibits phospholipase Cβ1-mediated hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP_2) by sequestering PIP_2 in lateral membrane domains[48]. Therefore, reductions in MARCKS membrane binding would also be predicted to increase Gqα-linked receptor-initiated hydrolysis of PIP_2 into diacylglycerol (DAG) and inositol triphosphate (IP_3) which increase PKC activity and intracellular calcium release, respectively. Moreover, free DHA inhibits PKC translocation and activity[49-52], and we previously demonstrated that perinatal deficits in DHA accrual were associated with significant alterations in the subcellular distribution PKC isozymes in the rat hippocampus[47]. Importantly, increases in PKC-mediated phosphorylation of MARCKS leads to a reduction in the tensile strength of the F-actin cytoskeleton and associated deficits in dendritic spine formation and stability[53]. Moreover, higher brain DHA levels are associated with elevated dendritic spine density and resilience[54-56], whereas perinatal deficits in DHA accrual are associated with reductions in synaptic connections[24]. It also relevant that elevations in PKC activity have been implicated in dendritic spine loss in response to chronic stress[57] and chronic inflammation[58,59]. Together, these findings suggest that DHA promotes synapse maturation and stability by decreasing PKC-mediated dismantlement of the F-actin cytoskeleton within synaptic terminals (Figure 1).

In addition to playing a role in the formation of new synapses, PKC, MARCKS, and the F-actin cytoskeleton also play a role in neurotransmitter vesicle trafficking and release efficacy within mature presynaptic terminals[60]. A role of DHA in this dynamic process is supported by findings of alterations in neurotransmitter vesicle distribution within presynaptic terminals[61,62] and abnormalities in the release, *i.e.,* increased basal release and deficits in stimulated release, of multiple neurotransmitter systems including dopamine[63-65], serotonin[66], and acetylcholine[67,68] in the DHA-deficient rat brain. It is relevant therefore that a dyregulation in dopamine[69-73], serotonin[74,75], and acetylcholine[76,77] have been implicated in the pathophysiology and treatment of mood and psychotic disorders as well as neurocognitive impairment. Increased glutamatergic synaptic efficacy is required for the induction of long-term potentiation (LTP) and the formation of new axodendritic synaptic connections subserve the maintenance of LTP[78-80]. Importantly, deficits in DHA accrual during perinatal development are associated with impaired LTP and a significant reduction in glutamate synapses in the rat hippocampus[24]. LTP is also thought to mediate the consolidation and storage of new memories[81,82], and perinatal deficits in DHA accrual are associated with impaired learning on hippocampus-dependent spatial learning tasks[83-85] and olfactory discrimination tasks[86-88]. Together, these

findings provide additional support for a role of cortical DHA in activity-dependent synaptic plasticity and synaptogenesis.

Critical to the "fine tuning" of cortical circuits during postnatal development is the pruning of extraneous and aberrant synapses. For example, during the peri-adolescent period there is a substantial (approximately 50%) pruning of glutamatergic connections between the rat frontal cortex and the amygdala[89]. While there is currently little known about the role of DHA in cortical synaptic pruning, in the developing rat visual system DHA deficits were associated with aberrant axonal innervation outside the main terminal zones of the superior colliculus which was transient and consistent with a delay in synaptic pruning[90]. It is also relevant that synaptic pruning is mediated in part by microglial phagocytosis[91,92], and a recent study found that DHA application to cultured microglia stimulated phagocytosis (M2 phenotype) and decreased the production and secretion of pro-inflammatory cytokines including TNF-α (M1 phenotype)[93]. The latter study also demonstrated that DHA application increased microglia BDNF biosynthesis, which was positively correlated with microglia phagocytosis, and BDNF expression is reduced in the frontal cortex of DHA-deficient rats[21]. A second study found that deficits in brain DHA accrual during perinatal development increased microglial pro-inflammatory cytokine production in the neonatal rat hippocampus, consistent with a non-phagocytotic pro-inflammatory phenotype[94]. These preliminary findings suggest that deficits in brain DHA accrual during perinatal development may disrupt synaptic pruning by altering the phenotype of microglia.

An important aspect of cortical circuit maturation is the myelination of axons, and DHA accumulates in myelin during perinatal rat development[17,95]. While there is currently little known about the role of DHA in the maturation of myelin sheaths and axonal conduction, intracerebroventricular administrations of either EPA or DHA in 2-day-old rats increased the expression myelin-related genes in different brain regions[96]. However, maternal FO supplementation, as well as maternal *n*-3 fatty acid deficiency, during pregnancy and lactation was found to impair auditory brainstem responses in neonates which was interpreted as a slowing of neural signal conduction[97,98]. A subsequent study found that initially lower auditory brainstem responses dissipated by young adulthood[98]. Another study found that maternal DHA supplementation during pregnancy and lactation impaired auditory startle response in neonates[95]. In adult rodents increasing dietary LC*n*-3 fatty acid status is protective against inflammation-[99] and trauma-induced[100,101] axonal white matter injury, as well as histopathological features in the experimental autoimmune encephalomyelitis model of multiple sclerosis[102]. While these preliminary findings suggest that there are optimal DHA levels required for normal axonal white matter integrity and resilience, additional research is needed to evaluate the role of perinatal brain DHA accrual on myelin integrity and circuit connectivity.

PRIMATE NEURODEVELOPMENT

Consistent with rodent studies, DHA concentrations increase sharply in the developing monkey brain during perinatal development[103,104], and baboons born preterm exhibit cortical DHA deficits compared with term births[105,106]. Primate perinatal *n*-3 fatty acid deficiency is associated with deficits in visual attention[107], polydipsia (excessive thirst)[108], and deficits in visual acuity and electroretinogram abnormalities[103,104]. Electroretinogram abnormalities have also been observed in neonatal baboons born preterm[109]. Consistent with dysregulated dopamine activity, perinatal *n*-3 fatty acid deficiency is associated increased home cage stereotypy and locomotion bouts[110]. A recent neuroimaging study found that resting-state functional connectivity among prefrontal cortical networks was impaired in young adult monkeys raised on an *n*-3 fatty acid deficient diet compared with monkeys raised on FO-fortified diet[111]. Specifically, *n*-3 fatty acid deficient monkeys exhibited reduced connectivity between the dorsal anterior insula (seed region) and ventromedial prefrontal, orbitofrontal, dorsolateral prefrontal cortices as well as with superior temporal sulcus and medial parietal areas. Although not specifically investigated, tracer studies demonstrate monosynaptic connections between monkey orbito-frontal cortex and amygdala[112]. Together these findings suggest that uncorrected deficits in cortical DHA accrual during perinatal brain development leads to reduced connectivity within prefrontal cortical networks in young adult non-human primates.

HUMAN NEURODEVELOPMENT

During human neonatal development, DHA accumulates in brain tissue at a rapid rate during the third trimester in association with active periods of neurogenesis, neuroblast migration, differentiation, synaptogenesis, and gray matter expansion[113,114]. Importantly, the third trimester of gestation is also a period associated with the initial formation of connections between brain regions including the uncinate fasciculus and superior longitudinal fasciculus[115]. Postpartum the neonatal brain continues to grow from approximately 350 g at birth to approximately 925 g at 1 year of age[116], during which DHA represents approximately 9% of total cortical fatty acid composition[1,117]. Neonates are wholly reliant on maternal breast milk (or formula) as the sole source of DHA. Term infants fed formulas without DHA consistently exhibit significantly lower erythrocyte and postmortem brain cortex DHA concentrations relative to breastfed infants or infants fed formula containing DHA[118-125]. The recognition that human breast milk DHA represents an important source for postnatal infant

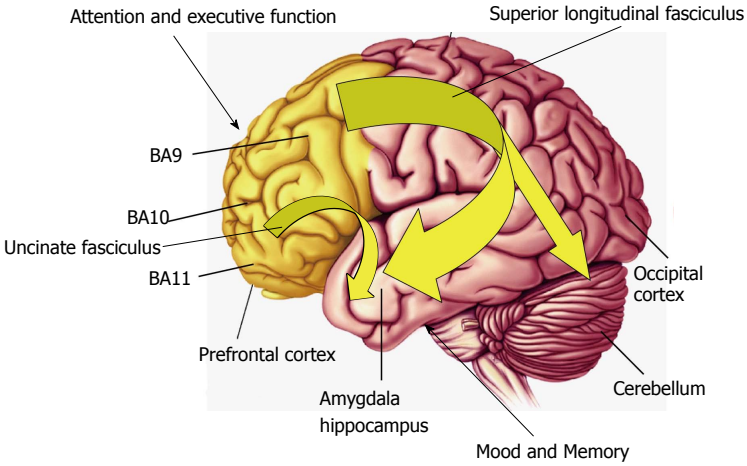

Figure 2 Diagram illustrating connectivity between frontal lobe regions, including the dorsolateral prefrontal cortex (Brodmann area 9, BA9,) and orbitofrontal cortex (BA11) which regulate attention and executive function, and temporal lobe structures including the amygdala and hippocampus which regulate mood and memory. Frontal lobe connectivity with limbic structures is mediated in part by the uncinate fasciculus and superior longitudinal fasciculus which develop during gestation and undergo significant maturation during childhood and adolescence. Reduced frontal circuit connectivity is exhibited by DHA-deficient non-human primates, children and adolescents born preterm, and patients with psychiatric disorders including ADHD and bipolar disorder which are associated with DHA deficits. DHA: Docosahexaenoic acid; ADHD: Attention deficit/hyperactivity disorder.

brain DHA accrual led to the widespread commercial availability of DHA-fortified infant formula in the United States in 2002.

During early childhood development DHA levels continue to increase in the frontal cortex[1] in association with linear increases in frontal cortex gray matter expansion and myelination[9-11,115], and the maturation of frontal lobe-mediated neurocognitive processes including attention and executive function[10,126]. During adolescent development cortical DHA levels continue to increase to approximately 15% total cortical fatty acids in young adulthood[1], and this increase coincides with frontal cortex synaptic pruning[127-129], white matter expansion and maturation[9-11,130,131]. Human neuroimaging studies indicate that the childhood and adolescent period is associated with the maturation of frontal cortical regions that mediate attention and executive function and the maturation of uncinate fasciculus and superior longitudinal fasciculus functional connectivity between frontal regions and limbic structures that mediate mood including the amygdala[9-11](Figure 2).

As observed in non-human primates[106], human infants born preterm exhibit lower erythrocyte and postmortem cortical DHA concentrations compared with term infants fed the same ALA-fortified formula postpartum[113,114,122,132,133]. Structural imaging studies have found that children and adolescents born preterm exhibit significant reductions in frontal and temporal cortical gray matter volumes, reduced amygdala and hippocampal volumes, reduced corpus callosum and white matter volumes, and enlarged cerebral ventricles[134-142]. Reductions in preterm cortical brain gray matter volume are correlated with functional connectivity deficits[143], and children, adolescents, and adults born preterm exhibit reduced connectivity within prefrontal cortical networks and decreased white matter integrity in different tracts including the uncinate fasciculus and superior fasciculus[144-155]. Importantly, deficits in white matter integrity have been observed in preterm born children with no neonatal ultrasound evidence for intraventricular hemorrhage, periventricular leukomalacia, low-pressure ventriculomegaly, or cytic white matter injury[145]. While these imaging findings suggest that deficits in third trimester DHA accrual may be associated with long-standing deficits in cortical circuit maturation, additional research is needed to determine whether early DHA supplementation can prevent or reverse these deficits.

Studies have also found that decreased white matter integrity in children and adolescents born preterm are associated with cognitive impairment and psychiatric symptoms[145,156-160]. Children and adolescents born preterm exhibit a significantly higher incidence of attention deficits, impulsivity, learning disability, language impairments, hyperactivity, anxiety, motor impairments, and poor social functioning relative to age- and sex-matched term children/adolescents[161,162]. Importantly, preterm birth and/or low birth weight is associated with increased risk for developing attention deficit/hyperactivity disorder (ADHD) in childhood[161,163-165] and mood, anxiety, and psychotic disorders during adolescence and young adulthood independent of multiple confounding variables including maternal history of psychiatric illness[163,166-170]. These findings suggest that deficits in cortical circuit maturation resulting from preterm birth are relevant to the etiology of ADHD in childhood and mood and psychotic disorders during adolescence and young adulthood.

While the contribution of DHA deficits to neurological and cognitive impairments commonly observed in preterm infants and children is poorly understood,

fortifying human milk or formula with higher levels of DHA is associated with improvements in visual acuity, sustained attention, and recognition memory compared with infants receiving DHA-free formula[171-174]. However, a systematic review of randomized controlled trials studying the effects of DHA-fortified formula for preterm infants concluded that there was no consistent effect on infant cognition or visual function[175]. It is notable, however, the DHA doses used in the majority of studies (0.2%-0.3% DHA) may have been too low to compensate for intestinal malabsorption, DHA oxidation, and early central DHA deficits in preterm infants. Indeed, a dose-response study found that milk DHA concentrations of 1% were required to increase DHA status in preterm infants to levels similar to term infants[176]. Moreover, deficits in cortical DHA concentrations in preterm baboons were not fully restored to control levels following 4 wk feeding formula fortified with a moderate dose of DHA (0.61%)[106]. It is also relevant that a placebo-controlled structural MRI study found that feeding formula containing lower levels of DHA (0.34%) did not significantly alter white matter volume in premature infants[177], whereas a preliminary intervention study observed improvements in brain white matter volumes in neonates with peroxisomal disorders following supplementation with higher DHA doses (100-600 mg/d)[178]. These and other findings have led to new recommendations for higher dose DHA supplementation for preterm infants to improve neurological and cognitive outcomes[179].

Prospective longitudinal studies have investigated the relationship between fetal cord blood DHA levels and neurodevelopmental outcomes in older children. These studies have found that higher LC*n*-3 fatty acid intake or cord blood DHA levels are associated with higher movement scores at 7 years of age[180,181], better neurological scores at 5.5 years[182], better visual function at 5 years of age[183], and better recognition memory and associated event-related potentials at approximately 11 years of age[184]. Another study found that higher cord blood DHA or LC*n*-3 fatty acid levels were associated with lower parent-reported hyperactivity/inattention and emotional symptoms among 416 children at 10 years of age[185]. A longitudinal study also found that higher cord blood DHA status was associated with lower levels of internalizing emotional problems including depression and externalizing conduct problems among 393 children at 7 years of age in subjects fed DHA-free formula but not those fed human milk[186]. The latter finding suggests that increasing postnatal dietary DHA intake can mitigate the emergence of psychiatric problems in youth exposed to low DHA levels *in utero*. Together, these data suggest that lower cord blood DHA levels are associated with an enduring negative impact on neurocognitive development.

Neonates become wholly reliant on maternal breast milk (or formula) as the sole source of DHA. Human breast milk DHA concentrations are highly correlated with maternal dietary DHA intake[6,187,188] and vary widely across different countries in accordance with habitual dietary fish consumption, *e.g.*, approximately 0.17% of total milk fatty acids in the United States *vs* approximately 1.1% of total milk fatty acids in Japan[189]. Several studies suggest that longer breastfeeding duration, a putative surrogate for early postnatal DHA intake, is associated with improved white matter microstructure and volume[190,191] and better neurocognitive outcomes in childhood, adolescence, and adulthood[192-194]. Prospective and retrospective studies have also found that shorter breastfeeding duration is associated with increased risk for developing ADHD in childhood[195-198]. However, the latter studies did not determine breast milk DHA concentrations to evaluate contribution to functional outcomes and additional/alternative benefits of longer breastfeeding (*i.e.,* better mother-child attachment) may also play an important role.

To investigate the relationship between breastfeeding duration and indices of neuronal integrity and function, we conducted a pilot study using proton magnetic resonance spectroscopy (^{1}H MRS) in healthy boys (age 8-10 years, mean 9.1 ± 0.9 years, n = 38). Regions of interest included right and left dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC). Subjects were breastfed for an average of 9.83 ± 1.7 mo (range: 0-42 mo). Following a median split of breastfeeding duration, we compared children who had received ⩾ 12 mo (n = 16, mean duration: 20 ± 8.9 mo) of breastfeeding with those who had received < 12 mo (n = 22, mean duration: 2.9 ± 3.2 mo). There were no significant differences in demographic variables between groups. Children receiving ⩾ 12 mo of breastfeeding exhibited higher concentrations of *N*-acetyl aspartate (NAA), a putative marker of neuronal integrity, in the right DLPFC and ACC compared with subjects receiving < 12 mo breastfeeding (Figure 3). Children receiving ≥ 12 mo breastfeeding also exhibited higher levels of glutamate+glutamine (Glx) in the right DLPFC and ACC. These preliminary data suggest that longer durations of breastfeeding may be an important determinant of cortical functional integrity in brain regions mediating attention and executive function in healthy developing children.

In summary, evidence from animal studies suggests that normal brain development requires optimal levels of DHA which has neurotrophic and neuroprotective properties. A potential ultrastructural mechanism mediating the beneficial effects of DHA on synaptic maturation and axo-dendritic connectivity is increased F-actin cytoskeletal stability in pre- and post-synaptic terminals mediated through reductions in PKC activity. Additional evidence from non-human primate and clinical imaging studies suggest that low DHA levels during perinatal development may lead to long-standing impairments in functional connectivity in cortical networks as well as the emergence of cognitive impairment, hyperactivity/inattention and emotional symptoms in children. Taken collectively, these

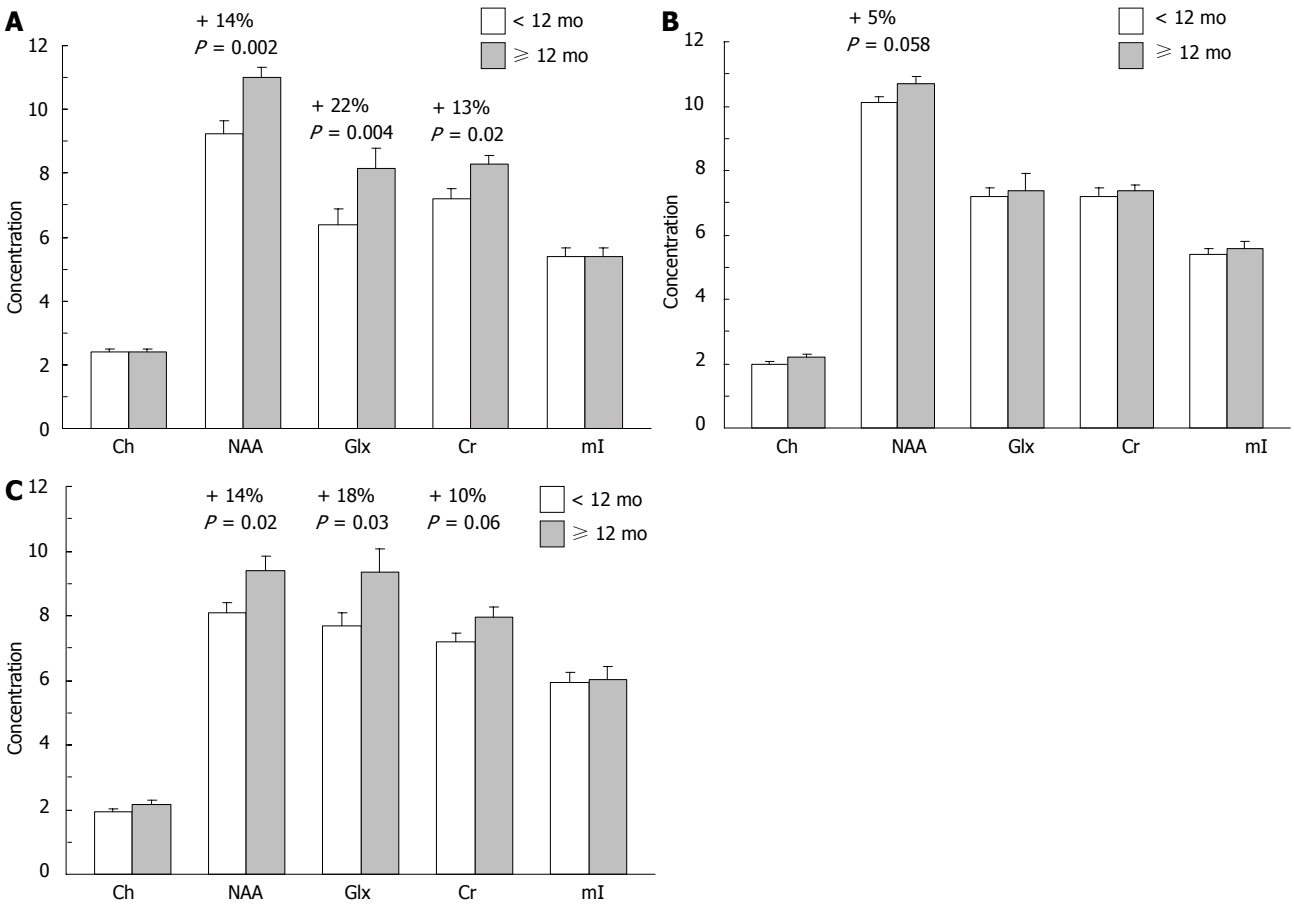

Figure 3 Mean concentrations of choline (Ch), N-acetyl aspartate (NAA), glutamate+ glutamine (Glx), creatine (Cr), and myo-inositol (mI) in the right dorsolateral PFC (A), left dorsolateral PFC (B), and anterior cingulate cortex (C) of children breastfed for < 12 mo (*n* = 22) or ⩾ 12 mo (*n* = 16). Note that NAA concentrations are significantly greater in the right dorsolateral PFC and anterior cingulate cortex of children breastfed for ⩾ 12 mo vs < 12 mo. Values are group means ± SEM. PFC: Prefrontal cortex.

associations support the assertion that cortical DHA accrual during perinatal brain development may play a role in the maturation of human cortical networks mediating cognitive and emotional processes.

IMPLICATIONS FOR PSYCHOPATHOLOGY

Major depressive disorder (MDD), bipolar disorder, schizophrenia, and ADHD are chronic and recurrent neuropsychiatric disorders that are a prominent cause of premature disability. The initial onset of ADHD typically occurs prior to seven years of age, and the initial onset of major mood and psychotic disorders frequently occur during adolescence or early adulthood[199-201]. Functional neuroimaging studies suggest that deficits in the functional maturation of frontal connectivity with limbic structures including the amygdala and/or the striatum are associated with psychopathology[202-206]. For example, event-related fMRI studies have repeatedly observed greater amygdala activation, and associated deficits in orbitofrontal activation, in response to emotional stimuli in youth and adults with bipolar disorder[207-209]. Although the initial onset of major psychiatric disorders commonly coincides with active and dynamic changes in frontal circuit connectivity, and psychopathology is associated with deficits in frontal circuit connectivity, a causal relationship has not been established. Moreover, the etiological mechanisms contributing to frontal circuit connectivity deficits in psychiatric disorders remain poorly understood.

Evidence from cross-national and cross-sectional studies suggests that LC*n*-3 fatty acid deficiency is relevant to pathophysiology and potentially etiology of different psychiatric disorders. Cross-national epidemiological studies have found that higher per capita intake of fish/seafood, a surrogate for LC*n*-3 fatty acid intake and status[210-212], is associated with lower lifetime prevalence rates of unipolar and bipolar depression[213-215]. Several population studies have similarly found that lower LC*n*-3 fatty acid intake is associated with increased risk for developing depressive symptoms[216-221]. It is also relevant that a large percentage of adolescents residing in western countries consume low quantities of LC*n*-3 fatty acids in their habitual diet[222-225], and lower LC*n*-3 fatty acid intake by adolescents is associated with a higher prevalence

of depressive symptoms[226-228]. Together, these data suggest that higher habitual dietary LC*n*-3 fatty acid intake may be protective against the development of mood dysregulation.

Habitual dietary LC*n*-3 fatty acid intake is highly correlated with erythrocyte membrane LC*n*-3 fatty acid levels[212], and multiple case-control studies have observed significant erythrocyte membrane LC*n*-3 fatty acid deficits in patients with psychopathology. A meta-analysis of 14 case-control studies found significantly lower erythrocyte EPA and DHA levels in MDD patients[229]. In bipolar patients, three independent studies have observed significant erythrocyte DHA deficits compared with healthy controls[230-232]. Importantly, erythrocyte DHA deficits have also been observed in pediatric and adolescent patients with MDD or bipolar disorder proximal to illness onset[233-235]. Medication-naïve first-episode psychotic patients exhibit erythrocyte DHA deficits compared with healthy controls[236,237], and a recent meta-analysis of 18 case-control studies observed significant DHA deficits in schizophrenic patients[238]. A recent meta-analysis of nine cross-sectional studies observed significantly lower blood DHA levels in ADHD children compared with healthy controls[239]. Together, these case-control studies provide evidence that different psychiatric disorders are characterized by low DHA status which coincide with, and may precede, the initial onset of psychopathology.

Dietary LC*n*-3 fatty acid supplementation has been found to significantly increase patient erythrocyte LC*n*-3 fatty acid levels[240-242]. This observation indicates that LC*n*-3 fatty acid deficits in psychiatric patients are modifiable by increasing dietary LC*n*-3 fatty acid intake. Importantly, meta-analyses of controlled trials have observed a significant advantage of LC*n*-3 fatty acid supplementation over placebo for reducing depressive symptoms in patients with MDD[243] or bipolar disorder[244]. Preliminary trials have found that LC*n*-3 fatty acid supplementation significantly reduces depression and manic symptom severity in pediatric and adolescent patients[235,241,242,245]. Accumulating evidence also suggests that LC*n*-3 fatty acid supplementation may be efficacious for the treatment of positive and negative symptoms in patients with or at ultra-high risk for developing schizophrenia[240,246,247], and for reducing attention deficits in pediatric and adolescent ADHD patients[239,248]. These data suggest that LC*n*-3 fatty acid deficits observed in patients with psychiatric disorders are correctable and associated with psychiatric symptom severity.

In general human erythrocyte and frontal cortex DHA levels are positively correlated[1], though non-human primate studies indicate that DHA recuperation occurs more rapidly in erythrocytes than cortical gray matter[2]. A growing number of case-control studies have investigated the fatty acid composition of postmortem frontal gray matter from patients with mood and psychotic disorders. Some studies have observed lower LC*n*-3 fatty acid levels[249-253] while others have not[254-256]. Our group reported that young adult patients with MDD[249], bipolar disorder[250], and schizophrenia[251] exhibit significant frontal cortex DHA deficits compared with controls. In a preliminary postmortem study, we also found that DHA composition increases sharply in the frontal cortex during normal human adolescent development, and that this increase is significantly blunted in young adult suicide victims[257]. It is also relevant that postmortem brain studies have observed reduced dendritic spine density and synaptic markers in the frontal cortex of patients with mood or psychotic disorders[258-260]. While these findings suggest that psychopathology may be associated with deficits in cortical DHA accrual and reduced synaptic density, limitations associated with the postmortem approach constrain interpretation[261].

Emerging evidence from structural neuroimaging studies provide additional support a beneficial effect of LC*n*-3 fatty acids on cortical integrity over the lifespan[262-266]. For example, one study found that greater habitual dietary LC*n*-3 fatty acid intake, which is positively correlated with erythrocyte DHA composition, was associated with larger cortical gray matter volumes in several corticolimbic regions including the anterior cingulate cortex, hippocampus, and amygdala[262]. It is relevant, therefore, that patients with psychiatric disorders commonly exhibit gray matter volume deficits in the anterior cingulate cortex, hippocampus, and amygdala[267-269]. Similar to children and adolescents born preterm, patients with ADHD[270-275], mood disorders[276-283], and psychotic disorders[284-287] also exhibit decreased frontal white matter tract integrity and reduced functional connectivity within cortical networks. Together these findings support the hypothesis that perinatal deficits in DHA accrual may contribute to diminished cortical circuit development observed in major psychiatric disorders.

The pathogenic mechanisms underlying major psychiatric disorders are viewed as polygenic and multifactorial, and there is strong evidence for familial transmission and subtotal heritability estimates indicating the important contribution of shared to-be-defined environmental factors[288-293]. Reviewed evidence supports a hypothetical link between dietary LC*n*-3 fatty acid deficiency and the familial transmission of psychopathology (Figure 4). Specifically, observational and controlled studies suggest that maternal DHA status during pregnancy is an important determinant of gestational length and risk of preterm birth[294-299]. For example, in Japan where maternal DHA status based on breast milk DHA levels (1.1%) is approximately 6-fold higher than breast milk DHA levels in the United Sates (0.17%)[189], the prevalence rate of preterm birth is approximately one-third that observed in United Sates (Japan: 4.3%-5.0% *vs* United Sates: 11.7%)[300,301]. Importantly, adolescent and young adult females of childbearing potential with mood disorders residing in the United Sates exhibit significant blood

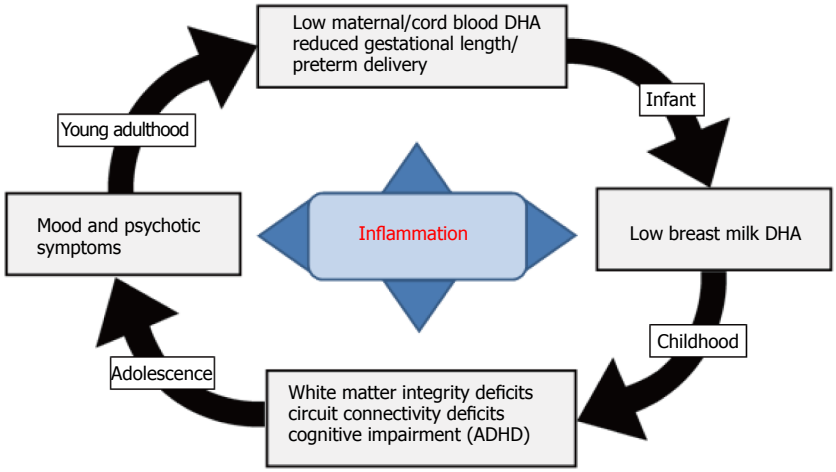

Figure 4 Diagram illustrating a hypothetical role of LCn-3 fatty acid deficiency in the familial transmission of psychopathology. Adolescent and young adult females with mood disorders exhibit significant blood DHA deficits leading to reduced fetal (cord blood) DHA accrual during pregnancy. Low maternal DHA status during pregnancy also increases risk for preterm delivery due in part to elevated pro-inflammatory cytokine levels, as well as low breast milk DHA levels postpartum. Uncorrected deficits in fetal brain DHA accrual lead to long-standing deficits in white matter resilience and integrity and reduced functional connectivity in fronto-striatal circuits and increase risk of developing ADHD symptoms in childhood. Deficits in white matter integrity and reduced functional connectivity in fronto-limbic circuits during adolescent development is associated with the emergence of emotional and/or thought dysregulation and the onset of mood and/or psychotic symptoms. DHA: Docosahexaenoic acid; ADHD: Attention deficit/hyperactivity disorder.

DHA deficits compared with healthy women[231,235], and are at increased risk for preterm delivery[302-304]. Risk of preterm delivery is associated with maternal or intrauterine elevations in pro-inflammatory cytokines including interleukin-6 (IL-6)[305-307], and lower LC*n*-3 fatty acid intake and status is associated with higher serum IL-6 levels[308]. The very low DHA status exhibited by mothers with mood disorders would be anticipated to reduce fetal cortical DHA accrual *in utero*, increase maternal risk for preterm birth and associated deficits in third trimester fetal cortical DHA accrual, and reduce postnatal fetal DHA accrual secondary to low breast milk DHA levels. Based the reviewed evidence, such perinatal deficits in cortical DHA accrual would be predicted to impair cortical circuit maturation and increase the risk of developing psychopathology during childhood and adolescent development.

CONCLUSION

Over the past 30 years a body of evidence from animal and clinical studies supports the general assertion that normal brain development requires optimal DHA levels. Rodent studies suggest that cortical DHA has neurotrophic as well as neuroprotective properties in the developing and adult brain, and that dietary-induced reductions in perinatal rat brain DHA accrual are associated with deficits in synaptic maturation and functional plasticity. Deficits in perinatal rat brain DHA accrual also lead to impairments on neurocognitive tasks requiring activity-dependent synaptic plasticity. Decreases in F-actin cytoskeletal stability in pre- and post-synaptic terminals, as well as reduced resilience against neurotoxic, synaptotoxic, and myelinotoxic insults, represent plausible mediating mechanisms. Non-human primate studies further suggest a link between *n*-3 fatty acid deficiency during perinatal development and long-standing deficits in functional connectivity in cortical networks, hyperactivity, and impairments in visual attention. Evidence from animal studies therefore provide strong evidence for a role of perinatal DHA accrual for the normal maturation of cortical circuits and provide important clues into candidate molecular and ultrastructural mechanisms.

Additional evidence for a role of DHA in normal brain development comes from human studies finding that preterm birth, which results in deficits in third trimester fetal cortical DHA accrual, is associated with enduring prefrontal cortical network connectivity deficits, and a spectrum of neurocognitive impairments which may be mitigated by postnatal high-dose DHA supplementation. Preterm birth is also associated with increased risk for psychiatric disorders including ADHD, psychosis, and mood disorders which are associated with deficits in functional connectivity within cortical networks. More direct evidence is provided by prospective longitudinal studies finding that lower cord blood DHA levels are associated with the emergence of cognitive impairment, hyperactivity/inattention and emotional symptoms in children. Moreover, longer breastfeeding duration (a putative surrogate for early postnatal DHA intake) is associated with improvements in white matter microstructure and volume and better neurocognitive outcomes in childhood, adolescence, and adulthood. Taken in conjunction with non-human primate imaging data, these associations suggest that cortical DHA accrual during perinatal brain development may play a role in the maturation of human cortical networks mediating cognitive and emotional processes that are dysregulated in psychiatric disorders.

It is not currently known whether LC*n*-3 fatty acid supplementation alone is sufficient to reverse deficits

in functional connectivity within cortical networks once established. Indeed, it is possible that cortical circuit maturation deficits secondary to LC*n*-3 fatty acid deficits may represent a permanent neurodevelopmental "scar" that is potentially irreversible once established. However, LC*n*-3 fatty acid supplementation has been found to reduce symptom severity in patients with psychiatric disorders and neurological and cognitive symptoms in preterm infants. Moreover, a controlled functional neuroimaging trial found that DHA supplementation increased cortical activity in prefrontal regions, and decreased activity in the temporal cortex and cerebellum, during performance of sustained attention task in healthy developing children[309]. While these findings suggest that increasing DHA status may augment functional connectivity within fronto-limbic networks, additional neuroimaging studies will be required to evaluate this potential therapeutic mechanism.

Although the role of perinatal brain DHA accrual on the maturation and long-term stability of cortical circuitry is only beginning to be fully understood, extant translational evidence suggests that DHA plays a role in the initial development and early maturation of cortical circuits. Emerging evidence from human neuroimaging studies further suggests that psychiatric disorders that initially emerge in childhood and adolescence and associated with low blood DHA levels are characterized by frontal circuit deficits compared with healthy developing youth. Moreover, maternal LC*n*-3 fatty acid deficiency is associated with increased risk of preterm birth, deficits in functional connectivity with cortical circuits, and ensuing cognitive impairments and mood dysregulation. These associations provide a neurobiological foundation and impetus for additional research to develop a more comprehensive understanding of the requirement for LC*n*-3 fatty acids during critical periods of neurodevelopment. Based on existing evidence, this research could have significant implications for informing novel early intervention strategies aimed at reducing the transmission of psychopathology.

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REVIEW

Smoking in schizophrenic patients: A critique of the self-medication hypothesis

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Abstract

A common remark among laypeople, and notably also among mental health workers, is that individuals with mental illnesses use drugs as self-medication to allay clinical symptoms and the side effects of drug treatments. Roots of the self-medication concept in psychiatry date back at least to the 1980s. Observations that rates of smokers in schizophrenic patients are multiple times the rates for regular smoking in the general population, as well as those with other disorders, proved particularly tempting for a self-medication explanation. Additional evidence came from experiments with animal models exposed to nicotine and the identification of neurobiological mechanisms suggesting self-medication with smoking is a plausible idea. More recently, results from studies comparing smoking and non-smoking schizophrenic patients have led to the questioning of the self-medication hypothesis. Closer examination of the literature points to the possibility that smoking is less beneficial on schizophrenic symptomology than generally assumed while clearly increasing the risk of cancer and other smoking-related diseases responsible for early mortality. It is a good time to examine the evidence for the self-medication concept as it relates to smoking. Our approach is to focus on data addressing direct or implied predictions of the hypothesis in schizophrenic smokers.

Key words: Nicotine; Nicotinic receptor; Dopamine; Positive-negative symptoms; Side effects; Age of onset; Smoking cessation

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Core tip: The high rates of smoking in mentally ill people have led to the uncritical acceptance that these individuals smoke to self-medicate with nicotine. A self-medication hypothesis (SMH) proposed three decades ago set the stage for explanations for smoking associated with mental illness. Here, we review the origins of the SMH and apply stated and implied predictions to smoking in patients. Our conclusions are that there is some support for the SMH explanations for smoking in schizophrenic patients.

However, there are sufficient contradictory data, and predictions not adequately tested, to justify continued empirical studies and new alternative hypotheses to the self-medication concept.

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INTRODUCTION

That smoking cigarettes is common among people suffering psychiatric disorders has given renewed popularity of the idea that patients may be self-medicating. Particular attention to self-medicating by smoking has been on schizophrenic patients.

The self-medication concept is reminiscent of an equally popular belief about cravings for certain types of food, given credence in psychology and physiology as "specific hungers"[1]. Anecdotal observations pointed to humans craving certain foods with pregnancy or other states accompanying marked changes in one's nutritional needs. The implication is that the person lacks a necessary nutrient and somehow that unconscious deficiency is transmitted into a specific hunger signal. Both the specific hunger and self-medication concepts recall the famous book by Cannon entitled "Wisdom of the Body"[2]. Subsequent research[3] and anecdotal observations question the generality of the concept.

The specific hungers concept also could be criticized by failures to identify neural mechanisms explaining nutrient deficiency inducing specific motivations. The self-medication concept, however, has that criticism covered. Plausible, neural mechanisms are well established that provide a means by which smoking could influence the brain. Nicotine is the major psychoactive component in tobacco and nicotine has a direct influence on cholinergic neurotransmitter pathways. Let us now turn to basics of the self-medication concept.

SELF-MEDICATION HYPOTHESIS

The initial formal presentation in the psychiatric literature of the self-medication hypothesis (SMH) often is attributed to Khantzian[4]. In an attempt to understand substance abuse, Khantzian noted clinical observations that the drug of choice by drug abusers is not random. Drug-dependent individuals under care for a psychiatric condition chose a drug related to the symptoms accompanying their specific mental disorder. Khantzian observed that cocaine is most often abused by psychiatric patients because of the stimulant qualities of the drug that "relieve distress associated with depression, hypomania, and hyperactivity"[4].

Thus, the self-medication concept could be described as being composed of several principles: (1) Diagnosed or undiagnosed mental disturbances precede initial substance use; (2) Mentally ill individuals are drawn to psychoactive substances more than are healthy people; (3) Deriving continuous symptomatic relief from the drug, the mentally ill person is led to excessive use with the consequence that they are disproportionally represented in addiction groups; and (4) The class of drug most attractive to the person is determined by the symptoms suffered by the person[5].

Although Khantzian's writings on the SMH remain focused on abuse of illicit drugs[6,7], the concept has been expanded to use of licit drugs, most notably alcohol and nicotine. For the latter, expansion was stimulated by epidemiological studies revealing that a remarkably high percentage of schizophrenic patients are regular smokers[8].

The SMH also has been expanded to suggest that smoking relieves psychiatric symptoms, but also the side effects of antipsychotic medications. Indeed, recent authors have emphasized the latter far more than the former to explain smoking by schizophrenic patients. The effects of nicotine on the brain and behavior would seem a plausible mechanism to alleviate well-known side effects of the medications, especially those induced by typical neuroleptics.

NEUROBIOLOGY OF NICOTINE

The most common form of self-administration of nicotine is smoking cigarettes. The main components of tobacco smoke are nicotine and the various particulate matters from the burning of tobacco collectively termed as tars.

Tars are carcinogens and responsible for most if not all smoking-related diseases[9,10]. Nicotine clings to tar droplets to be absorbed by tissues in mouth, nose, throat and, especially, alveoli of lungs. Over decades of smoking, these tissues begin to reveal pathology that often continues into development of disease states. The contribution of nicotine to tobacco-related diseases is its addictive properties that motivate the smoker to continue exposing himself to the tars of cigarettes[11].

Nicotine is the main neurologically active agent in tobacco. Nicotine from a puff of smoke is rapidly delivered to the brain *via* venous circulation, the left ventricle of the heart and then the arterial bloodstream. Time of this route to the brain is 10-20 s[12]. It is the rapid rise in blood levels and delivery to the brain thought to be key to addiction to a drug[13].

Nicotine binds nicotinic receptors that are targets for the endogenous neurotransmitter acetylcholine (ACh) in the peripheral and central nervous systems[14]. The nicotinic receptor (nAChr) is one of two subtypes in cholinergic pathways; the muscarinic subtype is the other one. There are also subtypes of nicotinic receptors[15], identified with Greek letters and numbers.

Cholinergic pathways have their origins primarily

in the basal forebrain cholinergic complex and the pontomesencephalotegmental cholinergic complex[16]. Cholinergic neurons, and nAChrs, are strategically positioned in forebrain, midbrain and hindbrain to influence most of the other neurotransmitters in the central nervus system (CNS), most notably the monoamines and amino acid transmitters[17,18].

A particularly striking feature of nicotine exposure is its capacity to increase the numbers of the nicotinic receptors in the brain. Findings in both humans and animal models have confirmed that long-term exposure to nicotine upregulates central nAChr numbers[19-21].

ACH, SMOKING AND THE NEUROPATHOLOGY OF SCHIZOPHRENIA

Schizophrenia is an intractable neurological disease most often first diagnosed after a psychotic episode in the late teens and early twenties. Although the worldwide prevalence rates of schizophrenia are likely less than the commonly cited 1%[22], patients are impaired in every aspect of daily functioning. Characterizing schizophrenia symptomology as positive (delusions, auditory hallucinations) and negative (anhedonia, apathy, cognitive degradation) have proven useful for treatment and prognosis[23].

Neurotransmitter systems have been a particular focus of research to identify underlying mechanisms of schizophrenia. Dopamine (DA) was the neurotransmitter initially implicated in the disorder. The DA hyperactivity hypothesis was proposed after revelations that the D2 receptor subtype was blocked by the original anti-psychotic medications[24,25]. Involvement of DA remains central to most schizophrenia hypotheses because only drugs that antagonize the D2 receptor are effective anti-psychotics[26]. The involvement of ACh in schizophrenia may be the capacity of nAChr to regulate dopamine activity[27].

Most commonly, activation of the nAChr increases the release of dopamine in DA pathways[28]. Nicotine interacts with DA neurons in midbrain sites that are the origins of projections to subcortical and cortical regions. The substantia nigra projects *via* the nigrostriatal DA pathway to the striatum and is considered a key to positive symptoms of schizophrenia. The ventral tegmental area sends DA projections to limbic and cortical structures. Activation of the mesolimbic pathway is likely the source of nicotine dependency. This pathway continues to the cortex as the mesocortical pathway, also known as the mesocorticolimbic pathway[29].

It was ultimately recognized that the DA hyperactivity hypothesis was too broad to describe the various features of schizophrenia. Patients often have abnormally high DA activity in nigrostriatal regions but abnormally low prefrontal DA activity[30]. A revision of the DA model concluded the negative symptoms are from prefrontal hypoactivity and the positive symptoms from striatal hyperactivity. The revision also explained the effectiveness of DA antagonist anti-psychotic drugs being most effective on the positive symptoms and less so on negative symptoms.

Other neurotransmitters and hypotheses emerged with the development of atypical anti-psychotic medications that antagonize serotonin (5-HT). Unlike the older, typical neuroleptics that normally do not provide improvement in negative symptoms, clozapine and other atypicals relieved both negative and positive symptoms in some patients. Because clozapine is both a dopamine and serotonin antagonist, these observations were followed by hypotheses for the involvement of 5-HT in schizophrenia[31].

More recently, glutamate hypoactivity has been hypothesized as contributing to the pathophysiology of schizophrenia[32]. Antagonists of the NMDA subtype of glutamate receptor leads to less stimulation of γ-aminobutyric acid (GABA) interneurons. The down-stream consequence is increased DA release in limbic structures[33].

Acetylcholine has emerged as another candidate neurotransmitter in the etiology of schizophrenia. Although antipsychotic drugs reduce some psychotic symptoms by antagonizing the D2 receptor, the medications have other pharmacological properties that may mitigate cellular mechanisms underlying the disease[34]. Indeed, several of the atypical anti-psychotic drugs show high affinity for ACh receptors[35]. Also, preclinical findings have confirmed interactions between ACh and DA. For example, nicotine binding of nAChr can influence DA release in cortical and subcortical areas[27,36].

SMH APPLIED TO SCHIZOPHRENIA

Khantzian's self-medication concept can be applied to cigarette smoking. Adapting the self-medication model to smoking by schizophrenic patients would appear to make specific predictions related both to the psychiatric symptoms of the disease and to the side effects of drug therapies used as treatments. Although not an exhaustive list, we have generated a set of predictions that appears in Table 1.

There are both direct and indirect findings in the literature in relation to all of these predictions. We now will review the evidence for each.

If smoking relieves symptoms in schizophrenia, patients should be more likely to smoke than healthy people

There is overwhelming evidence throughout the world that people with schizophrenia are more likely to smoke cigarettes than are healthy people[37]. The prodigiously high 80%-90% smoker rates cited in the literature and in popular media are questionable[38,39]. Nonetheless, the more reasonable figure of 60%-65%[8] is significantly higher than the approximately 25% prevalence rate among North Americans.

Moreover, a schizophrenic smoker consumes more cigarettes each day and with a greater preference

Table 1 Predictions for the self-medication hypothesis as applied to smoking in schizophrenic patients

Item	Prediction
A	If smoking relieves symptoms in schizophrenia, patients should be more likely to smoke than healthy people
B	Smoking behaviors and their effects in patients and healthy people should be different
C	Age of onset for regular smoking should correspond to the age of appearance of the first psychotic symptoms
D	Smoking and non-smoking patients should show behavioral differences
E	If smoking relieves side effects of antipsychotic medications, smoking in patients should change with drug treatments
F	If they smoke for reasons other than simply the addictive properties of nicotine, success of smoking cessation programs should be lower in schizophrenic smokers than in healthy smokers
G	Schizophrenic smokers who are successful at smoking cessation should experience worsening of symptoms of the disease or medications
H	The pathology of neurobiological systems (brain regions, circuits and neurotransmitters) underlying schizophrenia should be the same as those influenced by the nicotine in cigarette smoke

for unfiltered, high nicotine and high tar cigarettes than does a smoker in the general population[40]. Schizophrenics also extract more nicotine per cigarette than do healthy smokers[41].

That cigarettes and nicotine hold a unique sway over schizophrenic individuals is suggested by comparisons with other psychiatric patients. Schizophrenic patients are more likely to smoke than patients diagnosed with other psychiatric conditions[8]. These data stand in contrast to the use of other unprescribed drugs. Although alcohol and illicit drug use by schizophrenic outpatients are estimated at circa 50%, this is no higher than many other psychiatric populations. Individuals diagnosed with major depression, attention deficit hyperactivity disorder and post-traumatic stress disorder are also attracted to illicit drugs and alcohol at rates similar to schizophrenic patients[42].

Smoking behaviors and their effects in patients and healthy people should be different

As predicted by the SMH, there are differences between the responses of schizophrenic smokers and healthy smokers. Yet, the overall data are mixed, with some supporting the SMH and others contradicting the hypothesis.

Schizophrenic patients report that they smoke for many of the same reasons indicated by smokers in general. However, there are differences in the ratings of certain motivations. For example, schizophrenic patients highly rank the stimulant properties of cigarettes[43], suggesting they associate smoking with relief from schizophrenia symptoms or, more likely, from medication side effects.

Interestingly, two extensive studies on the motivation to smoke found that healthy controls more prominently cited increased social activity than schizophrenic smokers[43,44]. This is surprising because a prominent symptom of the disease is asociality, and one would expect relief from asociality would be attractive to patients. Indeed, an experiment designed to assess the social influences of nicotine failed to support the SMH. Schizophrenic and healthy smokers were administered nicotine after 24 h abstinence from smoking. There were no group differences on social cognition or facial affect recognition. Moreover, there were no differences in subjective stress reports[45].

This is in contrast to the conclusions of other authors that smoking schizophrenics are more sensitive to acute nicotine abstinence[46]. Upon finding abstinence-induced decrements in visuospatial working memory task only in the schizophrenic smokers, the authors concluded that patients experience greater cognitive declines than in non-patient smokers[47].

Other studies in this literature have used various measures of cognition to distinguish between schizophrenic and healthy smokers. Smoking in both groups has been reported to enhance some aspects of cognitive function, working memory and, especially, sustained attention to visual cues[48]. However, patients who smoke may benefit more; for example, schizophrenic subjects had better information processing scores than healthy smokers on a selective attention task[49]. A review of the cognition literature concluded that nicotine from smoking was effective in remediating many of the cognitive deficits accompanying schizophrenia whereas evidence for gains in cognitive performance in healthy smokers was more suspect[50].

Age of onset for regular smoking should correspond to the age of appearance of the first psychotic symptoms

A key principle for Khantzian in his SMH was that mentally ill individuals seek out drugs, including nicotine, to mollify the symptoms of their condition. We interpreted this to predict that non-smoking patients would initiate smoking upon development of full-blown psychosis. Yet that is rare. A report of 176 patients found that only few nicotine users had started after onset of psychoses[51]. More commonly, regular smoking of cigarettes precedes a schizophrenia diagnosis.

Timing of the onset of the smoking habit with onset of schizophrenia has been a fertile field for speculation. There is little doubt that the onset of smoking most often begins prior to diagnosis. The debates are about its meaning.

For many, the significant time lapse between smoking onset and psychosis is the most damning of the predictions from the SMH. Others have dismissed the age of onset differential as being expected because symptoms may appear before a formal diagnosis. Indeed, we know that adults who develop schizophrenia

may show distinctive neuromotor function as early as 2 years of age[52]. However, it is unclear how neuromotor activity is related to the array of cognitive, communication and motivational symptoms of adult schizophrenia[53].

Other symptoms that more closely match the disease could, of course, emerge and beginning the cigarette habit could correspond to first blush of those early and presumably subclinical symptoms. This is a position that resists careful scrutiny because the ontogeny of schizophrenia is unknown. It is difficult to know when schizophrenia begins. The premorbid stage is characterized by deficits shared by myriad other disorders[54].

The prodromal phase, the period when psychosis onset is not far off, for the distinguishing positive symptoms of the disease is unlikely to extend past 1-2 years prior to diagnosis[23]. As pointed out by Tandon *et al*[23], there is an unsubstantiated assumption that premorbid features are accurate precursors of the prodromal symptoms leading to schizophrenia. More striking is that most individuals with psychotic symptoms in a presumed prodromal phase do not go on to develop schizophrenia.

An imperfect attempt at an empirical resolution is to use retrospective data to identify the age of onset of smoking relative to age at which disruptive symptoms would have occurred. The literature offers some support for close timing of smoking relative to psychosis onset that supports the SMH while other reports do not.

Initiation of regular smoking has been cited to be about 2 years before the age of onset of schizophrenia[55], suggesting that smoking was within the time frame of the prodromal period. These data are consistent with an earlier report that the age of onset for smoking was 2.3 years before symptomatic onset[56]. Importantly, the latter study found that regular smoking was more closely tied to disease onset with schizophrenia than the 8.6 years differential observed with other psychotic diagnoses. Also, there is some evidence that prodromal symptoms and early psychotic episodes are associated with a progressive increase in smoking behavior[57]. Finally, a significant number of schizophrenic patients began regular smoking into their late thirties, which likely corresponds with manifestation of symptoms and, especially, chronic exposure to medications[58].

In opposition are studies reporting a longer differential between onset of smoking and schizophrenia, and the absence of data of initial symptoms when smoking was initiated. Most schizophrenic patients report they began smoking around the same age as healthy controls, *i.e.*, in their teenage years and well before the onset of symptoms[59]. Individuals diagnosed with schizophrenia, mood disorders and healthy controls reported similar onset of smoking for all three groups[58].

A study by Smith *et al*[60] poses a particularly strong challenge to the SMH prediction on the time from between onset of smoking and initial symptoms. Smoking history was assessed in a community-wide sample of 115 first episode patients. Of the 67 patients who smoked, 80% had started to smoke around 14 years of age. Yet, those individuals experienced functional declines or psychosis at around 19 years of age. The authors concluded, "In most cases, smoking preceded illness onset and was not a response to early features of illness[60]."

Another report was of schizophrenic patients starting to smoke during adolescence and at least 5 years before initiation of psychiatric medication. The authors interpreted their data as indicating that symptomology, anti-psychotic drugs or the prodromal period could adequately confirm an association between schizophrenia and smoking[61].

In a sample of 406 including both hospitalized and outpatient schizophrenics, there was no difference in the onset of the disease between smokers and nonsmokers[62]. In the same study, up to 90% of schizophrenic smokers reported the time between initiation of smoking and disease onset was circa 5 years. The conclusion was, "the psychotic phase of the disease per se is not the major factor leading to the increased frequency of smoking[62]."

Still others have raised the possibility that nicotine use itself might elevate the risk for developing schizophrenia. Supporting data are from longitudinal studies showing that beyond cannabis and alcohol use, early consumption of tobacco increases the risk for psychosis[63].

Finally, an important study by Weiser *et al*[64] examined records kept by Israeli agencies on adolescents to determine the onset of smoking and subsequent risk for schizophrenia. It represents the rarest of studies, a longitudinal study of smoking prior to diagnosis and, presumably, detectable symptoms of a mental illness. A random sample of adolescents were screened and determined to present no signs of a major psychopathology. The adolescents then were administered a questionnaire on smoking, finding that 28.4% smoked at least one cigarette per day. The cohort was followed for 4 to 16 years to determine development of schizophrenia (0.3%) and its relation to prior smoking. Findings were a significant linear relation between adolescence daily smoking levels and risk of developing schizophrenia during adulthood. The authors concluded early smoking was unrelated to symptomatic relief. The more likely explanation was that smoking worsens the neurophysiological bases for the disease in genetically susceptible people.

To summarize, all studies cited above agree that age of smoking onset begins well before symptom onset. That smoking onset is well before individuals were diagnosed with schizophrenia suggests to us that smoking was not in response to early symptoms. Still, one cannot dismiss that possibility completely.

What we can say without controversy is that onset of smoking prior to development of schizophrenia is unrelated to alleviating side effects of antipsychotic

medications. Smoking begins in patients long before they begin drug therapies.

Smoking patients should show different symptomology than non-smoking patients

On the question of behavioral differences between patients who smoke and patients who do not, the evidence is mixed. Support for the SMH comes from studies comparing cognitive performance, particularly improvements in attention. Conflicting data emerges from comparisons of the symptoms of smoking and non-smoking patients.

A battery of neuropsychological tests was used to assess the influence of an acute administration of nicotine to schizophrenic samples that did or did not smoke[65]. Across domains of learning and memory, language or visuospatial abilities there were no differences. The only domain to show improvement from nicotine was attention.

Deficits in attentional gating of sensory input are common symptoms accompanying schizophrenia. First episode schizophrenic patients not yet prescribed antipsychotic drugs were evaluated for sensory gating. Results indicated that both smoking and non-smoking patients showed worse sensory gating than healthy smoking or non-smoking controls. However, the smoking patients showed less of a sensory decrement[66]. This is one of the few reports that give us a glimpse into smoking prior to diagnosis and drug treatment. And the results offer support for the SMH in that prior smoking allays a common deficit in schizophrenia.

Another study tested schizophrenic patients and found smokers displayed improved attention performance over non-smoking schizophrenics[67]. These findings were also observed in first-episode psychosis (FEP) patients. Smokers scored better than non-smokers on attention tasks and also exhibited faster working memory reaction times[39].

Segarra *et al*[68] followed patients with first-episode psychosis during their initial year of antipsychotic treatment. At baseline, they found that smokers with FEP performed faster during a selective attention task than non-smokers. Although their reaction times were comparable to that of non-smokers, smokers exhibited fewer omission errors in a working memory task than non-smokers.

It is of interest that the smoking patients showed no cognitive improvements over the year. Cognitive performance of non-smoker patients, however, improved from baseline to 12 mo during the course of antipsychotic treatment[68]. And, although more smokers than non-smokers self-reported smoking as a means to improve concentration, their nicotine intake did not correlate with behavior in the attention paradigms[69]. These data suggested to the authors that "subjective or objective attentional benefits are unlikely the primary driving force of tobacco consumption" in schizophrenia.

Another paradigm in the literature is to test the possibility that smoking would be different in patients with predominantly positive and negative symptomatology. The interaction of nicotine with dopamine predicts that smoking would be more closely related to positive symptomology. Results have yielded every possible outcome with some reporting smoking related to positive symptomatology, to negative, to both positive and negative symptomatology[41,70] or to neither positive nor negative symptoms[51].

Aguilar *et al*[71] explored the association between frequency of smoking among Spanish schizophrenia patients and symptoms, medication side effects and outcome. Results were that mildly dependent smokers had fewer high positive symptoms and total PANSS (Positive And Negative Syndrome Scale for Schizophrenia) scores than non-smokers or, importantly, highly dependent smokers. The authors concluded, considering all of their data, they had found little support for the SMH.

Other reports suggest smoking may be related, rather than to schizophrenic symptomology, to depressive symptoms commonly comorbid with psychosis. For example, rates of smoking were found to be similarly elevated with schizophrenia and other psychotic disorders. Smoking was not associated with psychotic symptoms, but cigarette consumption over time covaried with depression[37].

Also, there were no differences in nicotine dependence between patients with schizophrenia and those with a mood disorder[58]. These data are notable because patients with schizophrenia complain far more about side effects than people treated with drugs for mood disorders.

There are other data suggesting that smoking worsen the symptoms of schizophrenia. In the Spanish cohort cited above[71] comparing positive symptom scores among smokers and non-smokers, highly dependent smokers had the most severe symptoms of schizophrenia. A recent report found that tobacco use and weight gain/obesity was associated with increased severity of symptoms of schizophrenia and decreased functioning[72].

Smoking of another substance, cannabis, also has been reported to be a risk factor for development of schizophrenia. High potency cannabis and frequent cannabis use was associated with an earlier age of onset of psychosis. Adolescents who used cannabis before the age of 15 were at a greater risk of developing psychosis earlier in life than their peers who began smoking at a later age[73]. Although there was a progressive increase in cannabis use upon onset of the prodromal phase[57], the self-report for reasons for smoking cannabis was mainly to enhance mood. Self-medication for symptomatic relief was ranked last[74].

If smoking relieves side effects of antipsychotic medications, smoking in patients should change with drug treatments

Should nicotine be able to relieve side effects of antipsy-

chotic drugs, smoking should either be initiated or increase after diagnosis. Early studies by McEvoy *et al*[75,76] are often cited as confirming the SMH. Typical antipsychotic drugs are more often accompanied by adverse side effects than are atypical antipsychotics. Smoking frequency should track a change in medications. Those were the results as schizophrenic patients switched from typical neuroleptics to the atypical drug clozapine, which decreased their smoking frequencies.

Later, de Leon *et al*[77] cast serious doubt on these findings. They addressed five of the basic conclusions of the previous studies. None of the five analyses demonstrated that clozapine had major effects on smoking. Indeed, by replicating the McEvoy *et al*[76] procedures as closely as possible, their findings of no relation between drug and smoking was a particularly striking repudiation of the SMH.

Matthews *et al*[38] reviewed the literature for evidence of the suggestion that atypical antipsychotics decrease smoking and promote smoking cessation while the typical medications may increase smoking and decrease the ability to stop smoking. However, the authors found that the studies used small sample sizes, were generally of moderate quality and reported conflicting data. Moreover, there are enough exceptions to question generalization to other antipsychotic drug classes[78].

Attempts to test the influences of smoking on the side effects of typical and atypical antipsychotic medications include assessment of extrapyramidal symptoms (EPS). Indirect support for relief of EPS comes from evidence that smoking decreases the effectiveness of antipsychotics. Smoking decreases serum levels of the atypical drugs clozapine and olanzapine, likely by increasing hepatic drug metabolism by activating enzymes of the cytochrome P450 enzymatic family[79]. It could be expected, then, that these patients would experience fewer side effects, should they be regular smokers, and those data have been reported[80].

The suggestion that smoking is a response to the side effects of antipsychotic medications has been questioned. Smoking and non-smoking schizophrenia patients did not differ on side-effect profiles with drug treatments. Incidences of tardive dyskinesia, for example, were the same in smokers and non-smokers[51]. Another study found no significant association between smoking in schizophrenic patients and antipsychotic usage or development of EPS[81].

A corollary of Prediction E is that if smoking relieves medication side effects, patients who are being treated with a drug producing fewer side effects should smoke less than drugs that produce more side effects. That question has been addressed and results supported the SMH. On a test of motivation to smoke, scores for sedative and anxiolytic effects of smoking were significantly associated with the dose and anticholinergic load of the medications[43]. Also, patients switched from the EPS-inducing typical medications to the atypical drug clozapine exhibit lower rates of smoking than those treated with typical antipsychotic drugs. However, the generalization to other atypical drugs, risperidone for instance, has not been confirmed[68].

More detailed analyses of smoking and atypical drugs have revealed another inconsistency. Among smokers and non-smokers, serum concentration of clozapine or olanzapine were reduced in the smokers. However, numbers of cigarettes smoked was unrelated to serum values. Patients who smoked 7-12, 13-19 or 20+ cigarettes per day had similar serum concentrations of the medications[82]. Because minimal smoking would relieve side effects similarly to heavy smoking, the elevated rates of daily smoking cannot be explained by the side effects prediction.

If they smoke for reasons other than simply the addictive properties of nicotine, success of smoking cessation programs should be lower in schizophrenic smokers than in healthy smokers

A clear prediction from the SMH is that mentally ill people have a greater dependency on the effects of nicotine on the brain. As a result, patients should have considerable difficulty stopping smoking. There is firm evidence that schizophrenic smokers have more difficulty quitting the habit than do healthy smokers[83].

With the well-known health consequences from long-term use, smoking is a concern for families and care providers of patients. Yet, smoking cessation rates among schizophrenic individuals are markedly lower than among both the general population and non-schizophrenic psychiatric patients[84]. Yet, the majority of patients say they would like to quit. Despite both internal and external motivations to quit, continuing to smoke suggests patients are accruing benefits from cigarettes[50].

Studies of the reasons for the cessation failure in schizophrenia focus on self-reports and type of drug therapy. Compared to healthy controls, patients self-report more often stress reduction, stimulation and increasing concentration[85]. However, the ability of patients to self-report accurately was questioned by an experiment using an attention task. Although participants with and without schizophrenia cited smoking helps their concentration, nicotine status predicted changes in attention in the healthy controls but not patients[69].

The similarly, high rates of smoking between people newly diagnosed and long-term patients suggests that drug treatments are not the cause of smoking. A similar case could be made for smoking cessation[59]. Type of antipsychotic medication has been examined in patients who were successful in cessation. Once again, the results are contradictory[38].

The general expectation was that atypical drugs would have fewer side effects and would promote

cessation. Although somewhat dependent upon the classification system used, successful smoking cessation did not align along typical-atypical medications. Rather, specific drugs appeared to be associated with smoking cessation. The atypical drug clozapine, but also various typical drugs, correlated to decreased cigarettes smoked per day[78]. Other atypical drugs, however, were relatively ineffective. The authors interpreted their findings as pointing to a greater blockage of the D2 dopamine receptor being a key to successful smoking cessation.

Schizophrenic smokers who are successful at smoking cessation should experience worsening of symptoms of the disease or medications

This prediction is possibly surprising, but it clearly follows logically from the SMH. It is based on the assumptions that smoking allays psychiatric symptoms of schizophrenia but only as long as the patient smokes. That is, smoking does not permanently change brain or behavior. Rather the current levels of nicotine determines reductions of symptoms.

There are anecdotal reports of exacerbated symptoms of schizophrenia following nicotine withdrawal[86], but systematic assessments on the influence of smoking cessation have revealed no major effect on the symptoms of schizophrenia[87]. Indeed, changes in smoking habits over years could not be linked to any systematic effects on symptom load, symptom improvement or subsiding of side effects[51]. Also, interventions that have proven effective in stopping smoking in individuals with mental illness do not appear to worsen psychiatric symptoms. Bupropion is a pharmacological treatment to aid smoking cessation in healthy people. When bupropion was employed to assist smoking cessation in schizophrenic patients, there were no change in their symptoms[88]. The interpretation is that the SMH failed in this basic prediction of the model.

The pathology of neurobiological systems underlying schizophrenia should be the same as those influenced by the nicotine in cigarette smoke

A prediction from the SMH is that the nicotine from smoking should influence the same brain regions and neurotransmitters that are pathological in schizophrenia. Results from studies of nicotine in animal models and some data from patients support the hypothesis. Yet, there are troubling inconsistencies in schizophrenia studies.

Much of the relevant research has focused on neural mechanisms underlying nicotine and the regional basis of different symptoms of the disease and of medication side effects.

Nicotinic ACh receptors are present throughout the human brain but in different concentrations in distinct brain areas. The highest density of nAChr are found in the substantia nigra, thalamus and caudate nucleus, and in moderate to- low densities in the frontal, parietal, temporal and occipital cortex, hippocampus, and cerebellum[89]. In contrast to conventional wisdom that an agonist down regulates receptor numbers, long-term nicotine exposure upregulates brain nAChRs. Postmortem binding studies have revealed increased binding sites in the brains of smokers compared to non-smokers[90].

Most commonly, activation of the nAChr increases the release of dopamine in DA pathways[28]. This provides a convenient mechanism for smoking to help relieve negative symptoms and cognitive deficits of schizophrenia. But, it proves troublesome for alleviation of the positive symptoms.

Recall that earlier we presented the dogma on dopamine and schizophrenia. Essentially, schizophrenics show hyperactivity in nigrostriatal DA pathways and hypoactivity in mesocortical DA pathways[30]. Importance of dopamine in the disease is highlighted by the well-documented findings that, although the different typical and atypical drugs influence different arrays of neurotransmitters, all effective antipsychotics block the D2 dopamine receptor subtype[91].

Hyperactivity of the nigrostriatal DA pathway is thought to be responsible for positive symptoms, explaining the clinical effectiveness of antipsychotic drugs' antagonism of the D2 receptor. Relative ineffectiveness of neuroleptics in treating negative symptoms is explained by DA antagonism presumably decreasing further the existing hypoactivity of mesocortical DA pathways.

Problems for the SMH emerge, first, when seeking to understand the attraction to smoking in unmedicated schizophrenics or individuals in predromal and prodromal stages of the disease. On the one hand, the neurophysiological data suggests smoking could help relieve the negative symptoms of the unmedicated person by opposing DA mesocortical hypoactivity. Nicotine would increase mesocortical DA activity and, consequently, prefrontal cortical function.

On the other hand, it makes little sense for unmedicated individuals to self-administer nicotine and further increase DA activity in brain regions impacted by an already hyperactive nigrostriatal DA pathway. Yet, we have seen subclinical symptoms as an explanation by the SMH for the onset of smoking being well before a schizophrenic diagnosis and drug therapy[60]. An outlet to resolve the dilemma would be to demonstrate that predromal or prodromal symptoms are primarily negative. However, we do not yet know the predominant symptoms of the individual when age of onset of smoking was years before diagnosis[92].

The SHM has been invoked to explain smoking to counter the adverse side effects of medication-induced reductions of nigrostriatal DA activity. Although perhaps predicted by the neurophysiological data, there is little evidence for greater relief of side effects of antipsychotics in patients who smoke[8].

The interested reader is directed to an excellent

review by Dome *et al*[87] for other neural data questioning the self-medication concept. Included is their observation that much of the support for the SMH comes from researchers funded by the tobacco industry.

The take-away for this final prediction is that smoking can modulate the same thought and emotional processes that are interwoven with the expression of schizophrenia[93]. Nicotinic receptors are found in brain regions that influence these same processes and chronic nicotine exposure has at least some effects that would appear to indicate a central involvement in allaying aspect of the disease[19]. However, there are inconsistencies in the findings and important data are lacking in the literature to conclude strong support for the neurophysiological predictions of the SMH. In particular, resolution of the dopamine effects on positive-negative symptomology will require clever experiments and insightful interpretations[94].

CONCLUSION

We generated a list of predictions from the self-medication hypothesis applied to smoking in schizophrenic patients. There are surely more predictions that could be generated from such a broad model. The ones selected here struck us as particularly relevant to the SMH.

We found support in the literature for certain predictions of the SMH. For example, patients smoke more than healthy people and, importantly, more than people with other mental illnesses. Patients cite reasons for smoking that are different from healthy smokers and that are related to symptoms of the disease. Smoking schizophrenics perform better on cognitive tasks, particularly attention paradigms, than non-smoking patients. And, there are neural mechanisms to support a self-medication concept.

On the other hand, we found the findings on age of onset of smoking relative to development of clear symptoms particularly troubling for the SMH unless unique and questionable assumptions are made about the early symptoms. Other creative interpretations of the neurophysiological data are required to resolve the opposing actions of nicotine-dopamine interactions on positive and negative symptoms. Finally, the evidence is conflicting that smoking patients have fewer symptoms than non-smoking patients. There are no data regarding a central component of the SMH, that is, that smoking allays undesirable side effects of antipsychotic drugs while leaving untouched the beneficial effects of the drugs.

Our conclusion is that there are sufficient data that appear contrary to expectations with the SMH explanation of smoking and to give us pause in continuing to accept the hypothesis without question. Our hope is that the generation of predictions presented in this review provides direction for future empirical tests of the SMH.

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REVIEW

Raising attention to attention deficit hyperactivity disorder in schizophrenia

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Abstract

Schizophrenia and attention deficit hyperactivity disorder (ADHD) are two psychiatric disorders with a negative impact on quality of life of individuals affected. Although they are classified into distinct disorders categories, attentional dysfunction is considered as a core feature in both conditions, either at the clinical then pathophysiological level. Beyond the obvious clinical overlap between these disorders, the Research Domain Criteria approach might offer an interesting perspective for disentangling common circuits underpinning both disorders. Hence, we review evidences regarding the overlap between schizophrenia and ADHD, at the clinical level, and at the level of underlying brain mechanisms. The evidence regarding the influence of environmental risk factors in the emergence of both disorders, and their developmental trajectories is also reviewed. Among these, we will try to elucidate the complex relationship between stimulants use and psychotic symptoms, discussing the potential role of ADHD medication in inducing psychosis or in exacerbating it. We aim that, taken together, these findings may promote further investigation with important implications both for clinicians and research. In fact, considering the amounting evidence on the overlap between schizophrenia and ADHD, the delineation of their boundaries might help in the decision for diagnosis and treatment. Moreover, it may help to promote interventions focused on the prevention of both schizophrenia and ADHD, by the reduction of recognized environmental risk factors.

Key words: Attention deficit disorder with hyperactivity; Central nervous system stimulants; Psychotic disorders; Schizophrenia; Toxic psychoses

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Core tip: In line with the translational approach of viewing disorders in terms of dysregulation of brain basic mechanisms, there is increasing evidence of overlap between different mental disorders. Here, we explore relationships between attention deficit hyperactivity disorder and schizophrenia, in light of recent insights into potential common etiological mechanisms explaining some of the observed overlap in both disorders. Using evidence from clinical epidemiology and neuropsychology, we propose a biologically-based reconsideration of these brain diseases. We have also summarized environmental risk factors for both disorders, aiming to promote awareness

regarding the need of appropriate interventions to prevent the onset and development of these diseases.

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INTRODUCTION

There is a mounting interest in discovering the links between neurodevelopmental disorders and psychiatric disorders in adulthood. Although the relationship between schizophrenia and attention deficit hyperactivity disorder (ADHD) has been poorly studied, it has been reported that the majority of individuals with schizophrenia, and their offspring, show early symptoms including attentional difficulties.

The concept of attention dysfunction in schizophrenia has changed over time, since the first descriptions of the disorder. Kraepelin made a distinction between active attention (*i.e.,* aufmerksamkeit) and passive attention (*i.e.,* auffassung) in schizophrenia, indicating with the former the ability to voluntary keep attention fixed for a period of time, whereas the latter concerned the attraction towards external stimuli[1]. Years later, these concepts have been called vigilance and distractibility respectively[2]. Also Jung explored cognitive features of schizophrenia. Using his word association task, he elaborated that attention of patients with schizophrenia appeared to be caught up in a series of feeling-organized ideas[3] , resulting from an internal distraction[4]. Jung's theory strongly influenced Bleuler.

In Bleuler's conceptualization, schizophrenia was characterized by two types of symptoms (*i.e.*, fundamental and accessory), and psychotic symptoms were considered as secondary to fundamental symptoms[5]. In fact, whereas accessory symptoms had a waxing and waning course, fundamental symptoms were more stable over time[5,2]. Regarding attention, Bleuler[5] reported that the tendency to fatigue sometimes was the cause of the reduction of attention.

Since impaired attention is a core characteristic of ADHD, and since the individuals who developed schizophrenia-spectrum disorders in adulthood have more often a history of childhood ADHD[6], it would be of interest exploring the relationship between ADHD and schizophrenia. In line with the focus of Research Domain Criteria project[7,8], we aim to use clinical epidemiological and neuropsychological findings as a point of departure for discussing the need of future investigation on potential common aberrations in fundamental neural system and neuropsychological functioning of these illnesses, that may impact on their treatment responsiveness, level of impairment and recovery processes.

CLINICAL EPIDEMIOLOGY

A history of ADHD symptoms has been commonly found in a sub-set of individuals who develop schizophrenia in adulthood[9-13], and ADHD is diagnosed in a high proportion of children at genetic risk for schizophrenia[14]. In the prospective longitudinal study of Kim-Cohen *et al*[15], more than 50% of adults with schizophrenia met the criteria for another psychiatric disorder in early adolescence, and ADHD, conduct disorder and oppositional defiant disorder were, among them, the most frequently reported. Moreover, a retrospective study performed by Rubino *et al*[16] found that a diagnosis of ADHD in childhood was most predictive of schizophrenia in adulthood compared to unipolar depression. Follow-up studies focusing on adult outcome of childhood ADHD[17,18] confirmed that youth with ADHD constitute a high risk group for developing a wide range of psychiatric diseases[17], and that children and adolescents with ADHD were 4.3 times more likely to develop schizophrenia later in adulthood compared to controls[18]. Moreover, females with ADHD presented a greater risk ratio for schizophrenia (RR = 20.1, 95%CI: 4.1-58.6), compared to males with ADHD (RR = 2.9, 95%CI: 1.1-6.8). Interestingly, duration of treatment with stimulants was not associated significantly with the development of schizophrenia[18]. Taken together, these findings indicate that children and adolescents with ADHD are at higher risk of developing schizophrenia than those who do not have ADHD.

NEUROPSYCHOLOGICAL FUNCTIONING

There are only a few studies comparing attentional dysfunction in schizophrenia and ADHD, and in some cases research findings are difficult to compare because of the definition of attention used, and also because of the varying methodology. As Luck *et al*[19] (2008) reported, the term "attention" has been defined so broadly in literature that it is difficult to compare the extent of attentional deficits among the disorders. Moreover, the interrelation between attention and other cognitive functions, such as working memory and executive functioning, it make difficult to isolate the attention deficit from disturbances in other cognitive functions. Another methodological concern is that studies performed in these groups typically use different versions of continuous performance tests (CPTs): whereas the CPT versions used in schizophrenia typically require the subjects to uphold vigilance to a multitude of stimuli, and to respond only to few of them, in ADHD the CPT protocol requires subjects to respond almost continuously[20,21]. This is because the goal is to investigate diminution in attention in schizophrenia, and to study the inhibition of impulsive responses in ADHD. Results show that adults with ADHD are more impaired to auditory

CPT compared to controls[22], presenting a slower reaction time, more errors of omission and late responses. Conversely, patients with schizophrenia present a reduced sensitivity without the increase of omission errors, considered measures of sustained attention[23,24]. Such differences have been suggested as reflecting distinct neurobiological underpinnings: a compromised ability to discriminate target from non-target noise stimuli in schizophrenia, and a difficulty in deciding if a stimulus is or not the target in ADHD[25].

Event-related potentials have been extensively used as measures of attention, and abnormalities have been found both in schizophrenia and ADHD. Specifically, patients with schizophrenia appear to be characterized by the inability to suppress the auditory event-evoked potential P50[25], by an amplitude reduction and a prolonged latency of auditory P3[26]. Since P50 alterations in P50 auditory evoked response-a measure of sensory gating-have also been found in first-degree relatives of patients with schizophrenia[27,28], in subjects with schizotypical personality[29], and in patients in remission who are not pharmacologically treated[30], dysfunction in sensory gating has been proposed as a potential biological marker for schizophrenia. However, a defective gating P50 is present also in other neuropsychiatric disorders, such as bipolar disorder[31,32], panic disorder[33], or post-traumatic stress disorder[34]. It seems that sensory gating dysfunction in schizophrenia has a genetic basis[35,36], and is associated with the chromosome 15q14locus of the gene encoding the α7 nicotinic receptor agonists[37,38]. Also the prepulse startle inhibition (PPI)-a measure of sensory motor gating-has been found impaired in schizophrenia, confirming the dysfunction in automatic or pre-attentional gating.

Moreover, altered visual N2 and P3[39,40] have been found in schizophrenia, although not in all studies[41,42]. N2 and P3 abnormalities are not specific to schizophrenia, having been also found in some studies with childhood ADHD[43-47]. A recent study performed on adolescents with early onset schizophrenia and subjects with ADHD on auditory oddball task and a visual go/no-go task found that the early schizophrenia group showed reductions in auditory oddball P3 and N2 amplitude, as well in the go/no-go visual P3[48]. Conversely, ADHD group showed a different ERP pattern, characterized by reduced visual N2 in the go/no-go task and a normal P3 amplitude in the go/no-go and auditory oddball tasks. However, previous results in ADHD[49-51] suggest that such P3 differences could be the results of developmental trajectories, tending to normalize with age[48].

PPI has been consistently reported as normal in ADHD[52-54], but a recent study found an abnormal P50 suppression also in ADHD[52]. This finding seems in line with the hypothesis that the attention deficit associated with ADHD may reflect a different neural substrate compared to schizophrenia.

Some studies have used measures of visual scanning in order to investigate the relationship between ADHD and schizophrenia. Indeed, even eye movements involve attentional processes, and increased anticipatory saccades are thought to represent an inability to select task appropriate behavior, which leads to increased task-inappropriate attentional shifts[55]. Deficits in early visual processing have been largely reported in schizophrenia[56-58]; studies of smooth pursuit eye movement have consistently shown greater anticipatory saccades in children of schizophrenic parents[55], adult schizophrenia[59,60] and children and adolescents affected by the disease[61] . However, increased premature saccades have been found also in ADHD during an oculomotor delayed response task[59,60]. Even though impairment in inhibiting responses to task irrelevant information seems to be present in both groups, patients with schizophrenia appeared to be more compromised, since it has been found they also have impaired selection of appropriate targets[59,60] .

Studies investigating affect recognition reported some differences in visual scanning style[62-64], and brain imaging studies seem to support the notion that impairment noticed in schizophrenia and ADHD involve different circuits. For example, perception of negative emotions in schizophrenia has been associated with decreased responses in both amygdala and medial prefrontal cortex[65,66], whereas a fMRI study performed by Hare *et al*[67] showed an amygdlar activation in subjects with ADHD during evaluation of negative emotions. Impairments in emotion perception in ADHD and schizophrenia may result from different abnormalities in prefrontal and subcortical circuits, key regions for emotional processing and also for motivational behavior. It would worthwhile to explore this further.

EPIGENETICS

A heritability estimate of 80% has been reported for schizophrenia[68], whereas it ranges from 60% to 80% in ADHD[69]. Although increasing evidence points towards the role of genetic factors in etiology of both schizophrenia and ADHD, environmental risk factors have been also explored and implicated[70,71]. Epigenetics concerns the functional modification of a genome expressions that is not associated with an alteration in sequence of the nucleotide[72]. Interactions between genes and environment are the basis of epigenetics, and are responsible for modifications in the expression of the genetic background of the individual, contributing to psychopathology[73]. In fact, potential epigenetic factors may confer risk for both disorders at various developmental phases, and environmental factors seem to have important roles in the etiology of psychotic illnesses both in pre- and post-natal periods[74]. Therefore, the early perinatal period is fundamental for proper brain development, and potential stress-inducing factors have been associated with schizophrenia, but also with ADHD[75,76].

Environmental risk factors

Studies on incidence and prevalence of both disorders show variations in rates according to place and time. Although this variance could be explained by the use of different methodologies and diagnostic classifications, analysis of these aspects may help to recognize potential environmental risk factors for the development of both these disorders.

A recent study performed on the health database of the Kaiser Permanente Southern California showed an ADHD prevalence rate of 0.36% in 2006 and of 0.65% in 2009[77], that is clearly in contrast with the overall prevalence of 2.9%-5.2% of the disorder as reported in adults[78]. In a meta-regression analyses to 135 studies, Polanczyk *et al*[79] found that differences in ADHD prevalence estimates could be mostly explained by methodological issues characterizing these studies. Therefore, the higher incidence of ADHD could be attributed to the lack of standardized assessment in most studies.

However, in literature some modifiable risk factors have been implicated in the pathophysiology of ADHD, which should be also taken into account. Among these, the most frequently mentioned are prenatal substances exposure, nutritional deficits and psychosocial factors[76]. Recently, low birth weight has been found significantly associated with ADHD even after controlling for environmental and genetic variables shared within twin pairs[80]. Prenatal maternal stress has been linked to increased risk of ADHD[81,82], and maternal smoking during pregnancy is the most cited among prenatal risks for the disorder[83,84], such as alcohol and illicit substances use during pregnancy[85]. Concerning nutritional factors, there are some controversial findings on the associations between low iron and ferritin and ADHD emergency, with some studies reporting such associations[86,87], and others do not[88,89]. However, deficiencies of folate, zinc, magnesium and polyunsaturated fatty acids have been shown to increase risk for ADHD[76,84].

Regarding schizophrenia, a review by McGrath *et al*[90] reporting incidence data for schizophrenia from 1965 to 2001, showed an incidence rate of 15.2 per 100000 and a range of 7.7-43 per 100000, suggesting an influence of environmental factors on these different rates, since genetic differences seem unlikely to explain such variations. Moreover, risk for schizophrenia seems to increase for individuals raised in urban areas, compared to those living in rural areas[91-93], providing support to the environmental hypothesis. Among peri-natal risk factors for schizophrenia, infections, nutritional deficits, toxins, and other sociocultural factors have been reported[71,94]. Infections during pregnancy with viruses such as rubella, varicella-zoster, polio, herpes as well parasites as toxoplasma, have been demonstrated to increase risk for the disease[71,95]. Maternal infections and inflammatory processes have been involved in preterm labor[96,97]. Obstetric complications are reported as factors contributing susceptibility for schizophrenia[71] and, as in ADHD, also in schizophrenia low birth weight was found associated with an increased risk to develop the disorder[98]. Although it is not possible to establish a causal effect, literature on nutritional deficiencies and schizophrenia susceptibility show some evidence of iron and vitamin D deficiencies as maternal risk factor for schizophrenia[71], such as a decreased choline[99]. Interestingly, considering that amniotic choline activates fetal α7-nicotinic acetylcholine receptors and promotes cerebral inhibition, it seems plausible that the increase of such activation through choline supplementation may protect infants from future mental diseases[100].

Stimulants and psychosis

In examining relationship between schizophrenia and ADHD, it is necessary to consider the fear regarding the potential of psychostimulants in producing psychosis or in increasing risk to develop schizophrenia. On this issue, literature reports controversial findings. A study reported that 77% of youth with psychosis had been exposed to psychostimulants[101]. The age of onset of psychosis was lower in subjects exposed to psychostimulants compared to non-exposed individuals[102], and there are some reports describing the emergence of hallucinations and delusions in ADHD induced by stimulant medication[103].

Both methylphenidate and *d*-amphetamine are considered effective and well tolerated pharmacological agents, and are still considered first-line choice for the treatment of ADHD[104]. Even though there is reluctance to treat patients with ADHD and psychosis with such medications, several studies show that stimulant treatment is safe. In fact, there are case studies demonstrating that stimulants have been well tolerated in subjects with psychosis, with or without concomitant antipsychotic treatment[105-109], with positive effects on cognition[110,111]. It has been suggested that the positive effect of methylphenidate, described in some studies, may be due to a regulation of frontal hypodopaminergic state[110,112]. In fact, methylphenidate affects dopamine D1 receptors in frontal regions improving cognition, whereas antipsychotics block D2 receptors in mesolimbic systems, without influencing D1 receptors[110]. On the other hand, it has been suggested that small but repeated doses of stimulants produce some alterations in the brain resulting in psychotic symptoms resembling schizophrenia[113]. This theory of sensitization has received support from some animal experiments[114], but has been also debated[115]. Curran *et al*[116] performed a systematic review investigating relationship between stimulant use and psychosis in humans. They examined 32 experimental studies, of which 28 involved the administration of a single dose of oral or intravenous dexamphetamine or methylphenidate to patients with schizophrenia. Their review reported evidence that a large administration of stimulant medication can produce a psychosis, usually lasting only some hours, and that positive symptoms

make individuals more likely to experience a worsening of psychotic symptoms. However, they did not found sufficient support for the sensitization theory, except in two studies[117,118].

Unfortunately, literature on adult ADHD as comorbid condition in psychotic symptoms is still scarce, and there is a lack of recommended pharmacological interventions for the treatment of patients affected by both conditions. Trying to differentiate some peculiarities of psychosis in presence of ADHD, Bellak *et al*[119] proposed a separate diagnostic category called ADD Psychosis. According to Bellak and colleagues, attention deficit disorder (ADD) could impact on the development of personality predisposing the individual, in some cases, to psychosis during the years of late adolescence or early adulthood, with distinctive features. In fact, ADD Psychosis was different from Schizophrenia because of rare or no hallucinations (that were brief and simple if present), concrete thinking (no thought disorder), poor impulse control, little or no social withdrawal, soft neurological signs, presence of dyslexia or dysgraphia, lack of response by neuroleptics, and favourable response to psychostimulants.

On the basis of case reports by Huey *et al*[120], Bellak *et al*[119], Pine *et al*[121], Opler *et al*[112] suggested a trial of psychostimulants in patients presenting both ADD and psychosis, with a poor response to neuroleptics. The cited studies show no worsening of psychotic symptoms but an amelioration of both attentional deficits and psychotic symptoms, probably by increasing perfusion to the frontal lobes[112].

In evaluating controversial results in literature regarding psychosis-induced by stimulant medication, Kraemer *et al*[122] suggested that psychosis in ADHD may be due to the combination of methylphenidate with other substance such as cannabis, alcohol, or illegal drugs. It is also possible that psychosis co-existed with ADHD, or even that psychosis was be the result of a undetected bipolar disorder, rather than to the stimulant treatment effect. Therefore, further research is needed in order to elucidate the potential of psychostimulant in producing psychotic symptoms. This is especially important considering that ADHD is currently recognized as a disorder affecting the entire course of life, consequently the use of psychostimulant medication could be continued over the lifespan[123].

Genetics and Neurobiology

The hypothesis regarding shared underpinnings between ADHD and schizophrenia has been supported by recent studies by Hamshere *et al*[124] and Larsson *et al*[125]. Such observation is consistent with an observation of an overlap in genetic susceptibility between ADHD and schizophrenia for rare copy number variants reported elsewhere[126]. Moreover, recent evidence from Hart *et al*[127] showed that SNPs associated with response to a dopaminergic drug challenge were enriched for those SCNPs associated with disorders usually treated with dopaminergic agonists (*i.e.,* ADHD) and antagonists (*i.e.,* schizophrenia), consequently SNPs nominally associated with schizophrenia and ADHD resulted associated with d-amphetamine response. They also found that the increased euphoric effects of d-amphetamine resulted associated with a decreased risk for both schizophrenia and ADHD. As has been suggested, these results provide support for the dopamine involvement in the pathogenesis of these disorders, and the acute amphetamine response may be further explored as an endophenotype for both schizophrenia and ADHD. However, it has been found a higher risk of a comorbid bipolar disorder rather than schizophrenia in people with ADHD[125]. This may be due to the fact that ADHD and bipolar disorder share more symptoms than ADHD and schizophrenia[128]. Irritability, distractibility, overactivity and impulsivity are very common among individuals with ADHD and/or bipolar disorder, and may therefore be of limited utility in differentiating the two groups, and their impact on the emergence of psychosis. Comparative studies examining common substrates across these disorders are warranted.

CONCLUSION

Until now only a few studies have made efforts to unravel the genetic and neurophysiological aetiology of ADHD symptoms in schizophrenia. It is still uncertain whether ADHD comorbid with psychosis constitutes a more severe subgroup of psychosis[129], or is an index of the severity of psychosis[102]. ADHD and schizophrenia share some features that require further investigation because it is possible that attentional disturbance characterizing both disorders may be fundamentally different.

The first difference of course is that attentional dysfunction emerges before 12 years of age in ADHD (DSM 5, APA 2013)[130], whereas this is not reported for Schizophrenia. Therefore, this difference has to be considered in the assessment.

Direct comparisons between these disorders will add to our knowledge of potential common aberrations in fundamental neural systems, and allow the identification of neural systems that are critical for the characterization of brain abnormalities and structural endophenotypes detectable by neuroimaging. Research is also needed in order to clarify the controversies regarding the differential diagnosis between BD and ADHD, and the relationship of these disorders with the emergence of psychosis in people using stimulant drugs.

Taken together, the findings reviewed above suggest the importance of screening for an ADHD diagnosis in neuroleptic refractory adult patients with psychosis. Although follow-up studies are warranted in order to have a better understanding of the risks and benefits of combining antipsychotics and psychostimulants in such clinical settings, the few studies, in which ADHD symptoms have been assessed in the second place,

did not report additional risk to the augmentation with drugs for ADHD treatment to antipsychotics in the stabilization phase. Deepening our understanding of the circuits underpinning these disorders may offer insights into phenotypes and more targeted interventions, which may also lead to plan early intervention and prevention.

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REVIEW

Assessment of psychological predictors of weight loss: How and what for?

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Abstract

Obesity is a multifactorial disease and the prominent factors playing a role in its pathogenesis are biological, environmental and psychological. There is a growing interest in understanding psychological functioning of obese subjects and the influence of psychological factors on treatment outcome. The aim of the present narrative review is to critically analyze the current literature, in order to point out the most common psychological constructs studied in obesity and to give an overview of the main existing tools investigating psychological features which have been considered significant for the prediction of success in weight loss and maintenance programs in obese patients. In this framework, the most common psychological constructs studied are: self-motivation, self-efficacy, locus of control, health related quality of life, self-esteem, self-control, concerns about body image, outcome expectations, and personality traits. These features have been explored through a wide variety of psychometric instruments. However, as an overall, studies evaluating the association between psychological features and treatment outcome failed to give consistent results. A possible explanation may consist on the fact that many tools widely used to explore psychological features were not specifically designed for obese patients and none of them was comprehensive of all possible psychological features involved. The identification of well-defined sub-groups of patients and the validation of more reliable and comprehensive tools, specifically designed for obese subjects, should be forecasted in order to reach a better knowledge of psychological functioning of obese individuals and to improve the outcome of weight loss programs.

Key words: Obesity; Eating behaviors; Psychometrics; Psychological assessment; Psychological predictors

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Core tip: A wide range of psychological conditions are bi-directionally linked to obesity. Psychological features may account for poor compliance and outcome in weight control programs but the current knowledge regarding this topic of research seems to be largely incomplete as

studies investigating whether psychological factors could be reliable treatment predictors failed to give consistent results. The aim of the present narrative review is to critically analyze current literature in order to better identify which psychological features can predict outcome in weight loss and maintenance programs, and to summarize the psychological tools most widely used for this purpose.

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INTRODUCTION

In the last decade obesity and overweight have become a global burden: the World Health Organization estimates that in 2005 approximately 1.6 billion people worldwide were overweight, 400 million adults were obese and at least 20 million children under the age of 5 years were overweight[1]. While in the foretimes overweight and obesity were widespread only in high-income countries, these conditions have now dramatically risen in low- and middle-income countries[2]. These countries are now facing a "double burden" of disease: they continue to deal with infectious diseases and under-nutrition, but they are also experiencing a rapid upsurge in risk factors for cardiovascular diseases and diabetes due to the increase of obesity and overweight. Experts believe that, if the current trend will continue, by 2015, approximately 2.3 billion adults will be overweight and more than 700 million will be obese[1].

Obesity has a number of serious consequences for individuals and governmental health organizations. In addition to the implications for the health of individuals, obesity enhances the risk of many diseases, which can contribute, directly or indirectly, to premature death and severe disability[3,4]. For this reason, overweight and obesity have a significant economic impact on health systems. The medical costs associated to overweight and obesity are represented by both direct (prevention, diagnosis, and treatment) and indirect costs (decreased productivity, restricted activity, absenteeism, and bed days).

Obesity is a complex disease since a great number of factors play a role in its pathogenesis: behaviors, environment, culture, socioeconomic status, genetic and biological features. All these aspects play a role and may have an effect in determining people to be overweight and obese[5]. However, the prominent factors involved in the recent worldwide epidemic diffusion of obesity are likely to be an increased intake of energy and the decreased physical activity or sedentary lifestyle[4]. It has been observed a global shift in diet towards energy-dense foods that are high in fat and sugars. Conversely, vegetables and fruits, which are rich in vitamins, minerals and other micronutrients, are less consumed, and this occurs along with a trend towards decreased physical activity[2]. For these reasons, it has been suggested that "obesity is the result of people responding normally to the obesogenic environments they find themselves in"[6].

In addition to environmental factors, also a genetic predisposition to obesity has been observed. Single gene mutations are responsible for rare forms of monogenic obesity[7] and common genetic variants of single-nucleotide polymorphisms may significantly increase the risk to develop obesity during lifespan[8,9]. Some of these obesogenic genes might also affect weight loss and weight loss maintenance. It has been demonstrated that polymorphisms of several obesity candidate genes have been shown to influence the outcome of weight management[9].

Psychiatric disorders and psychological features have been also reported as conditions which may play a significant role in developing obesity. With respect to psychiatric disorders, the highest comorbidity rates have been obviously reported for Binge Eating Disorder and other atypical Eating Disorders[10,11]. However, also Depression and Anxiety Disorders have been associated to obesity. This association seems to be bidirectional since depression and anxiety are associated with unhealthy behaviors including higher caloric intake, alcohol abuse and physical inactivity, which are risk factors for obesity. Conversely, obesity leads to an increased lifetime risk of both Depression and Anxiety[12,13] and it is well known that most of the antidepressant treatments can induce weight gain[14].

Moving to psychological correlates of obesity, some studies aimed primarily at identifying domains of psychological dysfunction associated with obesity have been published[15-17]. However, in the last years, the emphasis has shifted to look at the causal relationships between body weight and psychological distress and how this may affect treatment outcome[18]. Again, the association with obesity seems to be bidirectional: obese individuals face stigmatization and discrimination in many domains of their lives, and their psychological well-being is usually compromised[19]. On the other hand, it has been proposed that specific aspects of psychological functioning may increase the risk of developing obesity[20].

A significant proportion of obese patients do not display psychiatric comorbidities[15,21]. However, also in these cases, it has been hypothesized that the psychological asset may be strictly associated to unhealthy behaviors, to a fickle compliance and to a worse outcome of weight loss programs[22,23]. As unhealthy behaviors are considered the prominent factors in developing obesity, in order to improve the treatment of obesity, the processes that promote successful behaviors and the adoption of healthy

habits should be better acknowledged.

Despite the growing interest in understanding psychological functioning of obese subjects, the current knowledge regarding this topic of research seems to be largely incomplete. One of the main obstacles to research in the field of psychological features interfering with obesity onset and management is represented by the heterogeneity of potentially relevant factors, usually explored through a wide variety of psychometric instruments.

Given these premises, the aim of the present narrative review is to critically analyze the current literature, in order to point out the most common psychological constructs studied in obesity and to give an overview of the main existing tools investigating psychological features which have been considered significant for the prediction of success in weight loss and maintenance programs in obese patients.

PSYCHOLOGICAL FEATURES USED AS TREATMENT PREDICTORS AND THE MAIN TOOLS FOR PSYCHOLOGICAL ASSESSMENT

Psychometric instruments in the field of obesity research are used to evaluate the psychological health of obese patients before, during, and after treatment. Psychometric questionnaires are important to compare the results of different weight management programs, and to understand the connection between medical and psychological factors in obesity[24].

The identification of factors accounting for good compliance and positive outcome in weight control programs is a major topic of research. Psychological features seem to play a key-role in the treatment of obesity and have been frequently investigated in order to reduce the lack of compliance and to improve effectiveness of dietary treatment, suggesting that a good psychological functioning may be associated with higher success rates in treatment and that weight loss may be associated to beneficial effects on many different areas of psychological functioning[25].

The psychological constructs most commonly investigated are: self-motivation, self-efficacy, locus of control, HRQL, self-esteem, self-control, concerns about body image, outcome expectations, and personality traits. Table 1 summarizes the questionnaires which have been more commonly used for the evaluation of these psychological features, as well as their main acknowledged limitations (if reported).

Teixeira *et al*[22], in a comprehensive *review* summarizing studies published from 1995, has evaluated which psychosocial aspects can be considered as potential predictors of weight loss and weight management[22]. Authors organized these predictors into three groups on the basis of the evidence found in literature: (1) with consistent evidence; (2) with mixed evidence; and (3) with suggestive evidence. Only a few predictors met the criteria to be included in the first group: less previous dieting, fewer weight loss attempts, self-motivation, general self-efficacy (in contrast to eating-related self-efficacy), and autonomy[22].

SELF-MOTIVATION

Self-motivation is a trait-like construct conceptualized as "a behavioral tendency to persevere independently from situational reinforcements"[26]. The instrument most widely used to measure motivation in obesity is the Self-Motivation Inventory (SMI), which has been generated to predict adherence to therapeutic exercise in preventive and rehabilitative medicine programs[26]. SMI has been frequently used in literature and it has demonstrated to predict treatment success in weight loss programs[27].

Other questionnaires that evaluate self-motivation have been rarely used in the field of obesity. For this reason, they have not been included in Table 1. The Weight Loss Readiness Test[28], a questionnaire developed to assess weight loss readiness and motivation, failed to predict weight loss and weight maintenance[27,29]. Recently, a new questionnaire evaluating motivation and readiness to treatment has been created and validated[30]. This test seems to be capable to identify those individuals with high desire to overcome the problem and with low obstacles in pursuing the treatment. Under these conditions, obese patients reach the goal of loosing weight more frequently than obese subjects who did no display these traits. However, in a more recent study, the same authors found that the test seems to be capable to predict weight loss only in men, suggesting that in women, other psychiatric or psychological factors may play a greater role[31]. Since the questionnaire has been published in the last few years, it has not been widely used or tested in populations different from those used for its validation.

As already said, self-motivation has been considered as a predictor of success with consistent evidence[22] and the findings of Teixeira *et al*[22] are in agreement with earlier findings[27] and with more recent studies which reported an association of self-motivation with weight loss and weight loss maintenance (*e.g.*, Cresci *et al*[32]).

Furthermore, motivational interviewing used to increase motivation for change and to improve treatment outcomes, appears to enhance weight loss in overweight and obese patients[33,34].

SELF-EFFICACY

Bandura has defined self-efficacy as the combination of outcome expectancies and efficacy expectancies and has suggested that behavioral changes require both the belief that the changes will result in the desired outcomes (outcome expectancies) and the belief that each individual is capable of making the change

Table 1 Summary of the tests most commonly used in the evaluation of psychological condition

	Areas of evaluation	Uses	Domains/subscales	NO. of items	Limits
Self Motivation Inventory[26]	Self motivation	Community samples, clinical populations	Tendency to persevere, finish tasks initiated, maintain self-discipline, motivate oneself	40	Not specific for obese subjects Assesses only the trait-like construct of self-motivation Does not include specific items to investigate expectations about health or weight
General Self-Efficacy Scale[37]	General self-efficacy	Community samples, clinical populations		10	Not specific for obese subjects
Eating Self-Efficacy Scale[38]	Perceived control over food consumption	Dieting and/ or overweight individuals	Two dimensions of efficacy to control overeating: Negative affect, socially acceptable circumstances	25	-
Weight Efficacy Life-Style Questionnaire[39]	Self-efficacy in weight management	Patients with obesity	Five dimensions of efficacy for weight management: Negative emotions, availability, social pressure, physical discomfort, positive activities	20	Neither the total, nor the five subscales scores were associated with either program attendance or weight loss[57]
Internal-External Scale[46]	Locus of control beliefs	Community samples, clinical populations	-	23	Not specific for obese subjects Does not include specific items to investigate expectations about health or weight
Multidimensional Health Locus Of Control Scale[47]	Locus of control in relation to specific health conditions and behaviors	Community samples, clinical populations	Internality, chance externality, powerful others externality	18	Not specific for obese subjects Does not include specific items to investigate expectations about health or weight Individuals could no longer be classified as "internals" or "externals" (compared to other questionnaires evaluating locus of control)
Dieting Beliefs Scale[48]	Locus of control with respect to personal weight	Dieting individuals	-	16	-
Weight Locus Of Control Scale[49]	Locus of control with respect to personal weight	Dieting individuals	-	4	-
Medical Outcomes Study: Short Form-36[56]	Health-related quality of life	Clinical populations	Physical function, role limitations (physical), vitality, general health perceptions, bodily pain, social function, role limitations (emotional), mental health	36	Not specific for obese subjects Does not measure disease-specific domains Lacks in sensitivity to detect small treatment effects It is recommended that it be used in conjunction with an obesity specific questionnaire[56] Does not include specific items to investigate expectations about weight Considers all individual psychological symptoms equally relevant in the determination of the patients' well-being
Impact Of Weight On Quality Of Life Questionnaire[57]	Health-related quality of life	Patients with obesity	Health,social/interpersonal life, work, mobility, self-esteem, sexual life, daily activities, living, comfort with food	74	Considers all individual psychological symptoms equally relevant in the determination of the patients' well-being
Impact Of Weight On Quality Of Life Questionnaire-Lite[58]	Health-related quality of life	Psychiatric patients, patients with obesity	Physical Function, self-esteem, sexual life,public distress, work	31	Considers all individual psychological symptoms equally relevant in the determination of the patients' well-being
Obesity Related Well-Being (ORWELL 97) Questionnaire[59]	Health-related quality of life	Patients with obesity	Perceived psychological status and social adjustment, physical symptoms and impairment	18	Weaknesses were found when trying to correlate Body Mass Index with sub-scores of the questionnaire

Rosenberg Self-Esteem Scale[65]	Global self-esteem	Community samples, clinical populations	-	10	Not specific for obese subjects Does not include specific items to investigate expectations about health or weight Measures global self-esteem and not the sub-domains of self-esteem
Tangney Self Control Scale[71]	General self-control	Community samples, clinical populations		36	Not specific for obese subjects
Three-Factor Eating Questionnaire-R18,-R21[76,77]	Domains of eating behavior	Community samples, obese individuals	Cognitive restraint, uncontrolled eating, and emotional eating	18; 21	
Body Attitude Questionnaire[87]	Body attitudes	Patients with eating disorders	Feelings of overall fatness, self-disparagement, strength, salience of weight, feelings of attractiveness, consciousness of lower body fat	44	Not specific for obese subjects Originally developed only for women
Body Shape Questionnaire[88]	Concerns about body shape and "feeling fat"	Community samples, patients with eating disorder	-	34	Originally developed for use in Anorexia Nervosa and Bulimia Nervosa Not appropriate for assessing body dissatisfaction in males
Physical Self-Perception Profile[89]	Self-evaluations in the physical domain	Community samples, clinical populations	Sport competence, perception of physical condition and fitness, perception of an attractive body, perception of physical strength, physical self-worth	30	Not specific for obese subjects
Body Cathexis Questionnaire[90]	Body dissatisfaction	Community samples, clinical populations	-	46	Not specific for obese subjects
Body Satisfaction Scale[91]	Body dissatisfaction	Community samples, patients with eating disorder, overweight subjects	-	16	Not specific for obese subjects
Body Parts Dissatisfaction Scale[92]	Body dissatisfaction	Community samples, clinical populations	Parts wished were smaller, parts wished were bigger, parts with which content	7	Developed for use in adolescents girls
Goals And Relative Weights Questionnaire[94]	Factors that influence selection of a weight goal, weight loss goals as “dream weight”, “happy weight”, “acceptable weight”, “disappointed weight”	Overweight and obese patients	-		-
Temperament And Character Inventory[107]	Normal and abnormal personality traits	Community samples, clinical populations	Novelty seeking, harm avoidance, reward dependence, persistence, self-directedness, cooperativeness, self-transcendence	240	Not specific for obese subjects
Karolinska Scales Of Personality[108]	Personality traits associated with vulnerability for psychological deviance	Patients with various psychiatric and psychosomatic disorders	Guilt, indirect aggression, irritability, suspiciousness, verbal aggression, inhibition of aggression, muscle tension, psychasthenia, psychic anxiety, somatic anxiety, socialization, social desirability, detachment, impulsiveness, monotony avoidance	135	Not specific for obese subjects Designed to evaluate abnormal personality, rather than variations of normal personality
Toronto Alexithymia Scale-20[111,112]	Alexithymia	Community samples, clinical populations	Difficulty describing feelings, difficulty identifying feeling, externally-oriented thinking	20	Not specific for obese subjects
Revised Neo Personality Lnventory[116]	Five broad personality domains	Community samples, clinical populations	Extraversion, neuroticism, agreeableness, conscientiousness and openness to experience; six specific facet scales in each of five broad domains	240	Not specific for obese subjects

(efficacy expectancies)[35,36]. Both general self-efficacy and eating-related self-efficacy have been measured in obesity research. The first one is mainly assessed using the General Self-Efficacy Scale (GSES) originally

developed by Schwarzer *et al*[37]. GSES measures how an individual judges his/her own competence in order to complete tasks (by the means of behaviors, thoughts, and emotions) and reach desired goals. Eating self-efficacy has been frequently assessed in obese individuals with the Eating Self-Efficacy Scale[38] and the Weight Efficacy Life-Style Questionnaire[39], which are considered useful tools to measure self-efficacy in obesity, especially for clinicians working with weight control programs. In fact, almost all the studies on self-efficacy have led to the conclusion that high self-efficacy towards eating behaviors is associated with success in weight management[40-44].

LOCUS OF CONTROL

Locus of control refers to the extent to which individuals believe they can control events affecting them. Locus of control is one of the four dimensions of core self-evaluations along with neuroticism, self-efficacy, and self-esteem[45]. The most commonly used instruments for measuring locus of control in obesity are the Internal-External (I-E) scale[46], the Multidimensional Health Locus of Control (MHLC) Scale[47], the Dieting Beliefs Scale (DBS)[48] and of the Weight Locus of Control (WLOC) scale[49]. The I-E scale was the first tool specifically designed to assess locus of control, but it does not include specific items to investigate expectations about health or weight.

In the last decades, a large body of literature has investigated the role of health-related control beliefs in influencing the course of chronic diseases, medication compliance and health promoting behaviors. The vast majority of studies have used different forms of the MHLC Scales developed by Wallston *et al*[47]. While the A and B forms were constructed to measure general health-related control beliefs without being specific to any health behavior or condition, form C was developed to investigate health-related control beliefs of individuals with an existing medical condition[50]. MHLC measures three possible localizations of health control: internal localization, called "internality" (internal locus of control, measured by a subscale named IHLC) and two external localizations called "powerful others externality" (measured by the subscale PHLC) and "chance externality" (measured by the subscale CHLC)[50]. Patients with high internality believe that their health status depends only on their own behaviors; patients with high powerful others externality are convinced that their individual health status is the consequence of the actions performed by powerful people, *e.g.*, doctors, family members, friends; patients with high chance externality believe that mainly chance, fate, or luck determine their health status[50]. Despite a large use of the MHLC Scale in obesity, information retrieved by its administration does not seem to add specific or accurate knowledge concerning weight-related control beliefs.

Two questionnaires more specifically designed for overweight and obesity are the DBS[48] and the WLOC scale[49]. These tests investigate weight-related control beliefs and have been frequently used in obesity research. Allison and Engel[51] reported that an internal locus of control is a beneficial trait regarding weight management and conclude that health- and weight-specific locus of control are more predictive than more general measures[51]. Wamsteker *et al*[44] found that less weight reduction is associated with the beliefs that obesity has a physical origin and is not under behavioral control. Wiltink *et al*[52] identified the attribution of overweight to eating habits as a factor predicting long-term weight loss in severe obese patients attending psychotherapy; whereas Nir and Neumann[53] found that an internal locus of control was related to a lower weight regain after a weight reduction program.

However, some studies failed to identify differences between "internals" and "externals" in terms of weight loss and weight maintenance[54].

QUALITY OF LIFE

HRQL refers to the "psychological, physical and social domains of health, seen as distinct areas that are influenced by a person's experiences, beliefs, expectations, and perceptions"[55]. Studies addressing HRQL as a pre-treatment predictor of weight outcomes have used instruments which may be divided into generic and disease-specific tools. The most widely generic tool used is the SF-36[56], which measures eight not-disease-specific domains. SF-36 has been frequently used in obesity research, but its main limitation consists in the fact that it has not been designed to detect the effect of overweight on quality of life (QoL)[5].

The instruments specifically developed for obese subjects include the Impact of Weight on Quality of Life (IWQoL) questionnaire[57] and the Impact of Weight on Quality of Life questionnaire-lite (IWQoL-lite)[58], which assess the effects of weight on QoL in eight areas and five areas, respectively; and the Obesity related well-being (Orwell 97) questionnaire[59], which assesses QoL across three areas and proposes that symptoms of similar intensity can have a different impact depending on the individual (items about the occurrence, severity, and relevance of each impairment on its own life are included in the test).

From one side, there is evidence that weight loss improves HRQL in obese subjects[60-62]. On the other hand, there is poor evidence for QoL as treatment predictor. Only few studies explored QoL as a predictor of success in obesity treatment and Teixeira *et al*[63] found an association between pretreatment quality of life measures and long-term outcomes of a lifestyle weight loss programs; whereas Rotella *et al*[31] did not confirm this result.

SELF-ESTEEM

Self-esteem has been defined as "a personal judgment of the worthiness that is expressed in the attitudes the individual holds towards himself"[64]. The main assessment tool used to evaluate self-esteem in obesity is the Rosenberg Self-Esteem (RSE) scale[65]. RSE measures global self-esteem, whereas other instruments such as the Coopersmith Self-Esteem Inventory and the Tennessee Self-Concept scale[64], which have been used only sporadically in obesity research (not included in Table 1), are multidimensional, as they measure self-concept (of which self-esteem is just one component) and the sub-domains of self-esteem (performance, social, and physical self-esteem).

Usually, clinical samples show lower self-esteem than community samples (both normal- and overweight)[66,67], and studies that investigated the impact of weight loss treatment on self-esteem typically report improvements in almost all its dimensions[68,69]. As a possible predictor of success, self-esteem has not been frequently investigated. However, a recent study reported that lower self-esteem may be related to unhealthy weight control behavior in women[70].

SELF-CONTROL

Self-control is the ability to refrain from acting on undesired behavioral tendencies[71]. The 36-item Tangney Self Control Scale measures general self-control and although it has been used in a number of studies to measure self-control in relation to eating behaviors and weight managment[72-74], the control over eating is often measured by using the revised shortened versions of the original Three-Factor Eating Questionnaire (TFEQ)[75-77], which measures three domains of eating behaviors: cognitive restraint (control over food intake to influence body weight and body shape), uncontrolled eating (tendency to lose control over eating when feeling hungry or when exposed to external stimuli), and emotional eating (propensity to overeat in relation to negative mood states). The two shortened versions have been developed in an obese population after it has been demonstrated that the original three factor structure lost its sensitivity in those samples[76].

Control over eating, measured with the subscales of the TFEQ, has been associated with weight reduction and successful weight maintenance[54,78-80], whereas a decreased eating restraint and increased in disinhibition have been found in those regaining body weight after the end of a weight loss program[81,82]. However, some studies failed to demonstrate the ability to predict weight loss based on pre-treatment TFEQ scores[83,84].

BODY IMAGE AND OUTCOME EXPECTATIONS

Body image is a multidimensional construct which includes: (1) the perceptual component, which refers to a person's skill to estimate precisely the actual size and shape of the body; (2) the attitudinal component, including one's cognitions and affect, having reference to the body; and (3) the behavioral component, which concerns a person's engagement in specific actions and the potential shunning of particular situations/environments[85]. The difference between the individual perception of his/her current body size and ideal body size is related to body satisfaction[86]. Up to 74% of obese patients have body image dissatisfaction and distortion[11], so this construct has been frequently assessed in pre-treatment psychological batteries. Several instruments are available to measure body image, concerns about body shape and body satisfaction. The most widely used are: the Body Attitude Questionnaire (BAQ)[87], the Body Shape Questionnaire (BSQ)[88], the Physical Self-Perception Profile (PSPP)[89], the Body Cathexis Questionnaire[90], the Body Satisfaction Scale (BSS)[91] and the Body Parts Dissatisfaction Scale (BPDS)(Corning *et al*, 2010)[92]. The BAQ explores a broad range of attitudes that subjects hold toward their body; its subscales encompass six distinct aspects of body experience. The BSQ is one of the most valid psychometric instruments for the assessment of distress related to body image and weight in obese individuals seeking weight reduction. The PSPP is widely used to measure self-evaluations in the physical domain and its validity has been supported in a wide range of samples; it assesses five subdomains of physical self-perceptions. The Body Cathexis Questionnaire assesses feelings towards various body parts or characteristics. In the BSS respondents are asked to rate each of 16 body parts on a seven-point scale ranging from "very satisfied" to "very dissatisfied"; the scale was designed for work in health-related fields: in particular the scale was used to assess body dissatisfaction in eating disorders and to monitor changes in body satisfaction in subjects undergoing surgical treatment for breast cancer[91]. The BPDS lists 7 body parts and asks whether there is a desire to change any part.

Finally, the Body Uneasiness Test[93] can be considered a really valuable tool to assess and measure body dissatisfaction. However, this test has been largely used only in Italy and for this reason it has not been included in Table 1.

More recent studies investigating possible predictors of weight outcome in obese patients used the Goals and Relative Weights questionnaire[94]. Briefly, this test takes into account weight expectations asking subjects to indicate their "dream" weight, and weight values that they would be "happy" with, they would consider "acceptable", and that they would be "disappointed" with, at the end of the weight loss program. The test does not include other areas of satisfaction or dissatisfaction linked to body weight or shape, and therefore it gives information of outcome expectations only related to the above mentioned parameter.

Many studies have found a link between body image, health and eating behaviors. Mond et al[95] suggested that shape concerns are an important mediator of the relationship between obesity and impairment in psychosocial functioning in obese women. Myers *et al*[96] found that obese individuals with higher rates of body dissatisfaction used more maladaptive coping strategies, Traverso *et al*[97] reported that body image is a pretreatment variable significantly associated to weight loss and Teixeira *et al*[63] reported that weight loss treatment completers displayed more positive scores for body image than non-completers. With respect to treatment strategies, Schwartz *et al*[98] identified body image intervention as a key point of weight loss treatments. Moreover, the tendency to evaluate oneself "worth" in terms of weight and shape has been identified as a factor characterizing the "weight regainers" in a retrospective study[99].

As already said, a dimension which is linked to body weight and image is "outcome expectations" in terms of weight modifications during treatment. The evaluation of outcome expectancies as possible predictors of weight loss has produced divergent results. Some authors have found that unrealistic expectations concerning weight loss frequently result in weight management failure and treatment discontinuation[9,63,100-102]. Conversely, different studies did not confirm these negative consequences of having unrealistic expectations for weight loss and weight loss maintenance[103,104] and did not support the hypothesis that obese patients should be encouraged to set lower weight-loss goals[105,106].

PERSONALITY TRAITS

Personality traits in the field of obesity research have been widely assessed using the Temperament and Character Inventory (TCI)[107] and the Karolinska Scales of Personality (KSP)[108]. The TCI was developed to provide a comprehensive evaluation of personality; it measures four dimensions of temperament (novelty seeking, harm avoidance, reward dependence and persistence) and three dimensions of character (self-directedness, cooperativeness and self-transcendence). On the other hand, the KSP was designed to evaluate abnormal personality, rather than variations in normal personality. It was originally developed to assess the personological traits associated to vulnerability for psychological deviance. In a number of studies personality traits in obese individuals have been assessed using the Five-Factor Model of personality (FFM, also known as the Big Five), which assesses five broad dimensions of human personality[109].

Alexithymic personality traits, which can be defined as the difficulty in describing feelings to others and in sharing inner experiences, are a psychological feature frequently observed in obese patients[110]. Alexithymia is usually assessed with the Toronto Alexithymia Scale[111,112].

A great number of studies have investigated the link between personality traits and weight loss with varying degrees of success. Teixeira *et al* in the above mentioned review reported that personality traits may be unrelated to obesity risk and weight management[22]. On the other hand, more recent studies have reported an association between personality traits and weight outcomes in weight loss programs: high scores in novelty seeking and low scores in reward dependence (assessed using TCI) were associated to decreased success in achieving weight loss; whereas the presence of lower narcissistic personality traits (assessed using TCI) has been reported as a positive predictor of weight loss[113,114]. Moreover, neuroticism has been associated to successful weight loss in obese patients following a very low energy diet[74].

A recent meta-analysis using inventories of the FFM and evaluating personality as a factor potentially explaining individual differences in long-term obesity risk or the likelihood of reversion from obese to non-obese, shows that the personality trait "conscientiousness" is robustly associated with the development and persistence of obesity[115]. Individuals with high conscientiousness are described as self-disciplined, task oriented and well organized, whereas low conscientiousness is characterized by poor self-control, impulsivity and lack of long-term planning[109]. Compared to individuals with low conscientiousness, individuals with high conscientiousness have almost 40% lower odds of being obese, and obesity was less persistent. Authors concluded that their findings lend support for conscientiousness being a prognostic factor for the reversion of obesity to non-obesity in initially obese individuals[115]. There is also evidence that individuals with high conscientiousness (measured with the revised NEO Personality Inventory which is intended to measure the Big Five personality traits[116]) lose more weight with pharmacological obesity treatment using orlistat[117].

Finally, in a study performed by De Panfilis *et al*[114], it has been suggested that obese patients with a co-occurent psychiatric disorders showed a poorer outcome when displaying higher alexithymic traits.

CONCLUSION

In obesity treatment, weight loss is very difficult to achieve and, once achieved, to maintain, and long term dietary compliance rates are usually very low. It is a matter of fact that more effective strategies to improve compliance rates for weight loss and weight maintenance are required.

Obesity is an heterogeneous and multi-factorial disease and pre-treatment psychological (as well as biological and environmental) differences among the obese subjects which are going to start a weight loss program may interfere with treatment outcome.

A major challenge for successful weight management is to specifically design weight loss programs to individual needs. It has been proposed that obesity

treatment should be individually tailored taking into account age, sex, degree of obesity, individual hormonal, metabolic and hereditary factors, but also to psychobehavioral characteristics[9]. A good assessment of the psychological functioning could be used to identify "what fits whom" and therefore match individuals to a compatible weight loss program that would maximize weight loss. On the other hand, it could also be useful to identify subjects that should be put out of treatment because their likelihood of success is estimated as very low. In both cases, a reliable identification of psychological predictors of weight loss could lead to more efficient treatments and could help public health services to save time and resources.

However, the use of instruments measuring psychological functioning to identify appropriate weight loss and weight management strategies just remains an intriguing possibility. To date, none of the above mentioned associations seem to be reliable enough to base treatment regimens on them. The lack of evidence on this field is due by both conceptual and methodological factors.

First of all, only a small number of the questionnaires described in this review have been specifically designed for obesity or for weight-related problems[38,39,48,49,57-59]. For this reason, in obesity research the same construct is often assessed with many different instruments across studies, which are usually not specific for obese subject. Furthermore, a tool designed to address the more significant psychological constructs "all in one" does not exist. In other words, the psychological tools used in obese population are often inadequate and too heterogeneous.

Authors' opinion is that research and clinical attention should be focused on two key-aspects: the definition of specific sub-groups of patients which may display different clinical features and psychological assets; and the identification of more reliable and comprehensive tools specifically designed on obese subjects. From one side these objectives could be reached through a wider and comprehensive psychological assessment of obese subjects, including features which are usually almost neglected in clinical settings. On the other hand, those traits which appear to be more strictly related to a better outcome in terms of weight loss and weight loss maintenance should be identified and highlighted during treatment programs for obese subjects. However, the final goal of this line of research should be to use these information in order to develop a specific psychometric instrument, more accurate in predicting responses to weight loss programs and which can be easily administered in a clinical setting, thus allowing clinicians to save time and energies and, at the same time, enabling sanitary institutions to save money.

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REVIEW

Effects of music and music therapy on mood in neurological patients

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Abstract

Mood disorder and depressive syndromes represent a common comorbid condition in neurological disorders with a prevalence rate that ranges between 20% and 50% of patients with stroke, epilepsy, multiple sclerosis, and Parkinson's disease. Notwithstanding, these conditions are often under-diagnosed and under-treated in the clinical practice and negatively affect the functional recovery, the adherence to treatment, the quality of life, and even the mortality risk. In addition, a bidirectional association between depression and neurological disorders may be possible being that depressive syndromes may be considered as a risk factor for certain neurological diseases. Despite the large amount of evidence regarding the effects of music therapy (MT) and other musical interventions on different aspects of neurological disorders, no updated article reviewing outcomes such as mood, emotions, depression, activity of daily living and so on is actually available; for this reason, little is known about the effectiveness of music and MT on these important outcomes in neurological patients. The aim of this article is to provide a narrative review of the current literature on musical interventions and their effects on mood and depression in patients with neurological disorders. Searching on PubMed and PsycInfo databases, 25 studies corresponding to the inclusion criteria have been selected; 11 of them assess the effects of music or MT in Dementia, 9 explore the efficacy on patients with Stroke, and 5 regard other neurological diseases like Multiple Sclerosis, Amyotrophic Lateral Sclerosis/motor neuron disease, Chronic quadriplegia, Parkinson's Disease, and Acquired Brain dysfunctions. Selected studies are based on relational and rehabilitative music therapy approaches or concern music listening interventions. Most of the studies support the efficacy of MT and other musical interventions on mood, depressive syndromes, and quality of life on neurological patients.

Key words: Music; Listening; Music therapy; Epilepsy; Narrative review; Stroke; Mood; Amyotrophic lateral sclerosis; Depression; Parkinson; Dementia; Multiple sclerosis; Neurological disease; Neurological disorders; Acquired brain injury

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Core tip: We conducted a search on PubMed and PsychInfo databases identifying 25 Randomized Controlled Trials or Clinical Controlled Trials regarding the effects of Music Therapy and other musical interventions on mood disorders in neurological patients. Although the Jadad score evaluation revealed a generally poor methodological quality of the research protocols, we found that almost all studies supported the effectiveness of musical interventions in improving mood, depression, quality of life, functional recovery, and neuromotor performances. Therefore Music Therapy and other musical approaches seem to be effective, inexpensive and non-invasive, being that no adverse side-effects were observed.

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INTRODUCTION

Neurology and psychiatry

Neurological diseases are often associated with several behavioral and psychological symptoms that are usually overlooked by neurologists because require diagnostic methods that differ from those used for classical somatic symptoms and are more suitable to the field of psychiatry. On the other hand, psychiatrists do not seem to give an adequate attention to these symptoms considering them as a consequence of a cerebral damage and more pertinent to neurologists. This clinical attitude is historically based on the obsolete and reductive distinction between "organic" and "functional" behavioral disorders introduced by the phrenologist George Combe in 19th century. According to Combe, cerebral diseases were respectively classified depending on the presence or the absence of cerebral lesions and from that time on this terminology has been used to indicate that some behavioral disorders are linked to a neurological damage while others are not. However, the reductionism of Combe's distinction clearly emerges from the clinical observation given that a wide range of nervous system's illnesses with different etiology shows both neurological and psychiatric symptoms. Emotional and behavioral disturbances with a polymorphic symptomatology are often connected to neurological disorders such as Multiple Sclerosis (MS)[1-3], Parkinson's Disease (PD)[4], stroke[5], dementia[6], traumatic brain injury[7], epilepsy[8,9], Amyotrophic Lateral Sclerosis (ALS) and others Motor Neuron Diseases (MND)[10,11], pain syndromes (like headaches) and can be observed even with or without "organic" neurological diseases, thus miming in some cases an idiopathic psychiatric disorder.

Most common psychiatric disorders in neurology are depression, anxiety, maniacal states, and thought and perception disorders. Other psychiatric syndromes that can be seen in persons with neurological disorders are alexithymia, worry, and locus of control[12]. For example, mood disorders are often associated with acute or chronic cerebrovascular pathologies where the most common complications is certainly depression, usually defined post-stroke depression (PSD). The frequency of this syndrome is variable accordingly to different studies with a mean of 40% of the cases[13] and data obtained by numerous studies seem to indicate the presence of multiple etiological factors, both structural-endogenous and environmental-external, that may change depending on the early or late onset of the depressive disorder. In addition, a bidirectional association between depression and neurological disorder may be possible being that depressive syndromes may be considered as a risk factor for certain neurological disorders. As sustained by two recent meta-analysis, depressive syndromes, particularly major depressive disorder (MDD), are associated with a significantly increased risk of stroke[14,15]. On the other hand, lower rates of depression in equally impaired orthopedic patients suggest that PSD may even result from a stroke-specific neurobiological change and not only from a consequence of the psychological distress or the related impairments[16-18].

The second most common neurodegenerative disorder is represented by PD, with a prevalence of 1% of the elderly worldwide population. About 30% of PD patients show clinically significant depressive syndromes and, again, it appears to be also an increased risk for depressed patients to develop PD[19-23].

As far as regard MS, depressive syndromes are psychiatric most common disorders associated to the illness. Among individuals with MS, relative to the general population, lifetime prevalence rates are elevated for MDD (36%-54%), bipolar disorder (13%), anxiety disorders (35.7%), adjustment disorders (22%), and psychotic disorders (2%-3%). Suicide may be at least twice as common[1].

Many reports of depression and its correlation with numerous variables in clinical samples of people with MS have been published. The few population-based studies have reported a high prevalence of depression, despite using different methods of data collection. The lifetime risk of major depression in people with MS has been estimated to be as high as 50% compared to 10% to 15% in the general population[24,25].

In a recent cross-sectional, population-based study conducted in Stockholm county, the authors reported a prevalence rate of depression of 19% [Beck Depression Inventory (BDI) > 13] among patients suffering of MS. It's interesting to note how depressive symptoms were associated with worse self-reported functioning, with poor memory function and with weak sense of coherence (SOC) (referring to "general resistance resources" - capacities that facilitate coping

with stressors). Moreover, the authors suggested to incorporate depressive symptoms or mental health as a standard parameter for assessment and follow-up in clinical MS management[26].

Data from the United Kingdom MS Register, those obtained directly from MS patients, confirmed a high rate of anxiety and depression: over half of the respondents (54.1%) reported anxiety and 46.9% reported a variable level of depression[27]. From this registry data were recently examined about the positive relationships between physical disability, anxiety and depression[28].

Other reports confirmed the need to recognize and treat, having widely effective treatments, several emotional disorders which may worsen functioning and quality of life, decrease treatment adherence, and increase risk of suicide[1].

The prevalence of depressive disorders is higher in MS patients than patients with other chronic disease, suggesting a possible direct effect of the illness on the pathogenesis of the depressive syndromes in addition to the reactive disorder. Some evidences suggested that depression in MS is largely biologically mediated by some of the same processes involved in the immunopathogenesis of this neurologic disease. In particular, the increase in proinflammatory cytokines, the activation of the hypothalamic-pituitary-adrenal axis, and the reduction in neurotrophic factors. Notwithstanding, depression and mood disorders still remain under-diagnosed and under-treated in neurological patients claiming for a bio-psychosocial model be used[29-32].

Music therapy

In last decades, a growing body of evidence in the use of musical intervention in clinical setting have been seen, concerning singing, music listening, musical improvisation, and other musical activities, as long as more structured music therapy (MT) treatments. Given that music engages a variety of brain areas involved in emotion, motivation, cognition, and motor functions, musical interventions have been used to increase socialization and cognitive, emotional, and neuromotor functioning[33-38]. Although the debate on what the boundaries of MT is still going on, different approaches of musical intervention are actually available referring to three principal domains: relational approaches, rehabilitative approaches and music listening.

Relational approaches refer to psychological models and involve both active and receptive techniques[39,40]. The former consist of different musical activities such as free or structured musical improvisation by means of simple musical instruments, singing, songwriting *etc*. that allow patient and therapist to directly interact building a musical relationship[41]. In receptive approaches music imagery and music listening are used to induce psychological beneficial effects and even to evoke and process emotions and thoughts[40].

Rehabilitative approaches, such as Neurologic Music Therapy (NMT)[42] refer to neuroscientific models and use primarily the potential of musical stimuli to activate perception and production areas in the human brain, providing a series of therapeutic applications to sensory, cognitive, and motor dysfunctions resulting from neurological disorders. Using directive approach based on a series of exercises, NMT may be used, for example, to improve gait and movements in post-stroke and PD patients[43-47] and language in persons with aphasia[48,49].

On the other hand, simple music listening interventions don't require neither a specifically trained therapist nor a direct therapeutic relationship with the patient being that beneficial effects are induced by the content of the musical stimuli and by the activity of listening itself. For these reasons, this practice is sometimes defined with the term "Music Medicine" rather than "MT"[41,50,51]. Notwithstanding, listening interventions seem to be quite common in clinical literature, usually based on self-selected or other-selected music proposed individually[52,53] or in group, as in the case of background music[54,55].

As far as regard neurological disorders, MT may promote functional recovery and also improve social and psychological outcomes such as socialization, motivation, mood, and depression[56]. Literature in this field shows that most of the musical interventions are currently used in clinical practice, being that the majority of the interventions are based on a combination of rehabilitative and relational techniques. Also music listening seems to be a common practice in neurological rehabilitation. Due to the possible side effects of pharmacological treatment of depressive syndromes following neurological disease, music and MT may represent a valid support in reducing depressive symptoms, improving mood and adherence to treatment while contributing to the functional recovery at the same time.

RESEARCH

PubMed and PsychInfo databases were considered for articles to include in the current narrative review. The research has been conducted by three independent reviewers using the following search terms: ("Music" OR "MT") AND (name of pathology) AND ("Mood" OR "Depression"). Names of pathologies where used alone or in combination with "OR" Boolean operator and included: "Stroke", "Parkinson", "Dementia", "Epilepsy", "ALS", "MS", "Cerebral palsy", "Neurological disease", and "Acquired brain injury".

We included only Randomized Controlled Trials (RCTs) or Clinical Controlled Trials (CCTs) studies in English language published in peer-reviewed journals between 1st January 1997 and 31st May 2014. Importantly, we considered only trials including outcomes concerning mood or depression where experimental conditions were clearly stated and consisted only or primarily of musical activities.

Assessments of methodological quality of selected studies have been provided using Jadad score[57]. Jadad scale is based on 7 items that evaluate three main characteristics of a clinical trial: the random assignment, the double-blinding of assessments, and the flow of participants. Scoring ranges from a minimum of 0 to a maximum of 5 points where a score of 3 indicates a good quality study. Being that 2 points on 5 are scored for double-blinding and none of the included studies had double-blinding assessment, the maximum possible score was 3. Even if it doesn't take into account allocation concealment and has been criticized for placing too much emphasis on blinding[58], Jadad scale represents a simple, easy and common way to evaluate the methodological quality of a clinical trial with good validity and reliability[59]. Due to the heterogeneity of the outcomes, no meta-analysis was carried out.

DESCRIPTION OF SELECTED STUDIES

A total of 464 records resulted from the search of which 301 from PubMed and 163 from PsychInfo. Twenty-five articles that met the inclusion criteria have been found and were included in the current review. Most of the selected studies are related to dementia (44%) and stroke (36%) while others regard MS, ALS/motor neuron disease, PD, Chronic quadriplegia, and acquired brain dysfunctions (20%). Fourteen studies (56%) employed a relational approach including both active and receptive techniques, six studies (24%) adopted a rehabilitative approach, and five (20%) concerned music listening interventions. Activities were conducted by trained music therapists in the most part of the experimental interventions. As far as regard the methodological quality of included studies, our analysis showed that only nine on twenty-five (36%) of the included studies received a Jadad score of 3 and thus can be considered of good quality. Five studies (20%) had a Jadad score of 2, three studies (12%) a score 1, and eight studies (32%) were evaluated with a score of 0. Results of the methodological assessment pointed out a general poor rigor in research protocols.

In the following subsections, results are presented through a subdivision of the selected studies by pathology (Tables 1-3).

Effects on dementia

Eleven studies assessed the effects of music and MT on dementia[60-70]. Eight studies employed a relational approach[60-61,63-65,68-70] based either on active or receptive techniques or a combination of both of them. Two studies concerned music listening interventions[62,67] and one study adopted a rehabilitative approach[66]. In most cases the results show a positive effect on mood, depression, and anxiety. Two studies revealed no significant effect of musical intervention[64,66] while in three studies both experimental and control group improved emotional and behavioral functioning in the same way[65,67,69]. Characteristics of the studies and main results have been summarized in Table 1.

Effects on stroke

Nine studies assessed the effects of music or MT on post-stroke patients[71-79]. Four of them were based on a relational approach[71,72,76,77], three regarded music listening interventions[74,75,78], and two used a rehabilitative approach[73,79]. All studies show a positive effect of music or MT on mood in patients with Stroke. For a synthesis of studies and results please see Table 2.

Effects on other neurological disorder

Five studies concerning other neurological disorders such as MS, ALS/motor neuron disease, PD, Chronic quadriplegia, and Acquired Brain dysfunctions, have been found[80-84]. Three studies concerned a rehabilitative approach[80,82,84] and two studies adopted a relational approach using an active technique[81] or both active and receptive techniques depending on what the therapist deemed appropriate in consultation with the patient[83]. All studies but one[83] reported positive effects of music and MT on outcomes as mood, depression, anxiety, and quality of life. Characteristics of the studies and main results have been summarized in Table 3.

DISCUSSION

In the last few decades, the development of neuroscience demonstrated that the brain isn't a static structure only influenced by genetic determinants but it is a plastic organ that continuously reorganizes synaptic connections under the influence of inner and outer factors such as genetic programs, environmental stimulation, learning and expertise[85-87].

Neurological illnesses that provoke behavioral disturbances might originate from both endogenous and external causal factors thus determining, depending on the circumstances, a more "structural" or a more "environmental" etiology. The mutual interaction between these factors occurs in the brain and gives rise to a variety of psychiatric disorders that can be distributed upon a continuum, on one end of which are behavioral disturbances clearly linked to neuroanatomic and neurochemical alterations while on the opposite those more associated to the environment.

Synaptic functions and neuroanatomic structures are proper "organic" factors that determine those alterations that are usually treated by neuropsychiatry and biological psychiatry. Behavioral disorders resulting from these factors include psychiatric syndromes that are linked to alterations of the neural transmission caused by receptor's abnormalities and by modifications of the synaptic concentrations of one or more neurotransmitters. Given that neurotransmitters regulate the neural impulse transmission processes into neurotransmitter systems, with a widespread projection in the

Table 1 Characteristics of the included studies concerning effects on dementia

Ref.	Design/ (Jadad)	Subjects	Diagnosis	Intervention	Professionals	Frequency	Outcome measures	Results
Ashida[60]	CCT (0)	20	Dementia	Playing percussion instruments and listening to live songs performed by the therapist	Music therapist	Five daily session of about 40 min each in a single week	CSDD	Significant reduction of depressive symptoms (P < 0.05)
Choi *et al*[61]	CCT (1)	20	Dementia	Singing songs, analysis of libretto, making musical instruments, playing instruments, song drawing, and song writing	Music therapist	50 min, 3 times 1 wk for 5 wk (15 sessions)	MMSE, GDS, GQoL, NPI-Q	Positive trends for GDS and GQoL in music group. Improvements in BPDS (P = 0.004) and caregiver distress (P = 0.003)
Guètin *et al*[62]	RCT (3)	30	Dementia (Alzheimer's type)	Weekly sessions of individual, self selected music listening. Control group underwent reading sessions	Not specified therapist	Once 1 wk for 18 mo for 20 min	HRSD, GDS	Significant improvements in anxiety and depression (P < 0.01) in the music therapy group
Raglio *et al*[63]	RCT (3)	20	Dementia	Active-intersubjective approach, based on sonorous-musical improvisation. Control group took part in educational and occupational activities without music	Music therapist	2 times a week for 15 wk for 30 min	ECG Holter, MMSE, ADAS-Cog test, NPI, ADL, IADL	Significant improvement of depression symptoms (P = 0.02) and increase of HRV (P = 0.013)
Cooke *et al*[64]	RCT (3)	47	Dementia	Musician-led familiar song singing and music listening. Control group participated in reading sessions	Musicians	3 mornings 1 wk for 8 wk for 40 min	DQOL, GDS, MMSE	Not significant effects on GDS and QOL. Positive trends in music group at sub-analysis
Fischer-Terworth *et al*[65]	CCT (0)	49	Dementia	Singing in group with the therapist, playing elementary musical instruments and listening to biographically relevant music. Control group participated in a nonspecific occupational therapy	Not specified	Once 1 wk for 6 mo for 45 min	NPI, ICEA-D, MMST, GDS	Depression decreased in both groups (P < 0.05). Improvements of NPI and ICEA-D (P < 0.01) in favor of music group No effects on mood. Improvements (P < 0.05) for MPI, MPD, attentional matrices
Ceccato *et al*[66]	RCT (3)	50	Dementia	Cognitive and sensorial exercises associated with musical stimuli	Music therapist	2 times 1 wk for 12 wk for 45 min	NPI, MPD, ADL, SVAM, GMP, MMSE, CMAI, GDS	No effects on mood. Improvements (P < 0.05) for MPI, MPD, attentional matrices, ADL, SVAM, and GMP
Janata[67]	RCT (3)	38	Dementia	Preferred music listening. Control group was incidentally exposed to the music programming in the course of daily life	Music therapist	Every day for 12 wk from 21 to 65 min	NPI, CMAI, CSDD, MMSE	Reduction of CSDD, NPI, and CMAI score in both groups (P < 0.0001)
Clemént *et al*[68]	RCT (2)	14	Dementia (Alzheimer's type)	Listening to music and playing hand-drums over recorded music. Control group underwent cooking activities. Both groups alternated receptive and productive phases	Psychologist with no musical experience	2 times 1 wk for 4 wk for 1 h	BEHAVE-AD, PSMS, SIB. EFE, Discourse contents and STAI-A	Short time effects of emotional indices (P < 0.05) and longer term effects of mood (P < 0.05) up to 4 wk after the end of the treatment
Narme *et al*[69]	RCT (2)	48	Dementia	Listening to music, singing and playing percussion instruments. Control group took part in cooking activities. Both groups alternated receptive and productive phases	Psychologist with no musical experience	2 times 1 wk for 4 wk for 1 h	SIB, NPI, CMAI, MMST, EFE, Discourse contents and STAI-A	Both group improved in emotional state, NPI score, and professional caregiver distress at different evaluation periods (P < 0.05)
Chu *et al*[70]	RCT (3)	104	Dementia	Song choice, music-prompted reminiscence, singing, music listening, and instrument playing	Music therapist	Two sessions per week for 6 wk for 30 min	C-CSDD, salivary cortisol, MMSE	Short time effects on depression (P < 0.001) and long time effects on cognition at 1 mo follow-up (P = 0.039)

ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADL: Activities of daily living; BEHAVE-AD: Behavioral Pathology in Alzheimer's Disease Scale; CCT: Controlled Clinical Trial; CMAI: Cohen-Mansfield Agitation Inventory; CSDD: Cornell Scale for Depression in Dementia; C-CSDD: Chinese Cornell Scale for Depression in Dementia; DQOL: Dementia Quality of Life; ECG Holter: Electrocardiography Holter; GDS: Geriatric Depression Scale; GMP: Good Manufacturing Practice; GQoL: Geriatric Quality of Life; HRSD: Hamilton Rating Scale for Depression; IADL: Instrumental Activities of Dailiy Living; ICEA-D: Inventory to Asses Communication, Emotional Expression and Activity in Dementia; MMSE: Mini-Mental State Examination; NPI: Neuropsychiatric Inventory; NPI-Q: Neuropsychiatric Inventory Questionnaire; RCT: Randomized Controlled Trial; SVAM: Metacognition Assessment Scale.

Table 2 Characteristics of the included studies concerning effects on stroke

Ref.	Design/ (Jadad)	Subjects (*n*)	Diagnosis	Intervention	Professionals	Frequency	Outcomes measures	Results
Purdie *et al*[71]	RCT[1] (0)	40	Stroke	Playing familiar or improvised music with the therapist by means of percussion instruments, synthesizers, or voice	Music therapist	Once a week for 12 sessions lasting 30-40 min each	FAST, HADS, MBRS, NRS	Positive trends in communication skills, behavior and psychological state in treatment group (not significant result)
Nayak *et al*[72]	RCT[2] (0)	18	Stroke or TBI	Singing, playing instruments, composing, improvising, listening	Music therapist	2 or 3 sessions a week during the hospitalization up to a maximum of 10 sessions	Face Scale, VAS, SIP, questionnaire	Positive trends in mood and significant improvements in social interaction ($P < 0.02$) and involvement in therapy ($P < 0.01$) in experimental group
Jeong *et al*[73]	RCT (2)	33	Stroke	Rhythmic motor activity with music based on Rhythmic Auditory Stimulation (RAS) theory (Neurologic Music Therapy)	Instructors	One weekly session of 2 h for 8 wk	ROM, POMS, SS-QOL, exit interview	Improvement in mood states and interpersonal relationship, flexibility, and range of joint motion ($P < 0.05$)
Särkämö *et al*[74]	RCT (3)	60	Stroke	Treatment group underwent preferred-music listening.A second group received self-selected audio book listening while a third control group had no listening material	Music therapists	Every day for 2 mo for 1 h (at minimum)	RBMT, WMS-R, BDAE, CERAD, Token test, BVRT, MBEA, FAB, POMS, SAQUOL-39	Improvements in depression ($P = 0.024$) and positive trends in confused mood with cognitive recovery (verbal memory and focused attention) in music listening group
Forsblom *et al*[75]	RCT(3)	39	Stroke	Preferred music listening. Control group underwent audio-book listening	Music therapist	Every day for 2 mo for 1 h (at minimum)	Analysis of patient's interviews	Improved mood, better relaxation, increased motor activity in music listening group ($P < 0.0001$)
Kim *et al*[76]	CCT (0)	18	Stroke	Hello song and sharing of events in their lives (5 m), planned musical activities (30 m) and sharing feelings and goodbye song (5 m)	Not specified therapist	Twice a week for 4 wk for 40 min	BAI, BDI, questionnaire of satisfaction	Improvement in depression ($P = 0.048$) and positive trends for anxiety
Jun *et al*[77]	RCT (2)	40	Stroke	Stretching exercises while listening to music, singing and/or playing songs on percussion instruments, and final verbalization	Researchers and music therapist	Three times per week for 8 wk for 60 min	ROM, K-MBI, K-POMS-B, CES-D	Improvements in mood states ($P = 0.04$) and increase in the degree of shoulder ($P = 0.03$) and elbow ($P = 0.04$) joint flexion
Chen *et al*[78]	CCT (0)	19	Stroke	Self-selected individual listening in two different conditions: pleasant music and unpleasant music. A white noise condition acted as control	Not specified	1 session for each condition, separated by no more than 1 wk[3]	VAS, HR, GSR, SCT, LBT, PST, visual task	Improvement of mood ($P = 0.03$) and arousal ($P < 0.001$) under pleasant music condition
Van Vugt *et al*[79]	RCT[4] (1)	28	Stroke	Play fingers exercises and children's song on the piano	Music therapist	10 therapy sessions for 3/4 times a week for 30 min	9HPT, Finger tapping measurements, POMS	Reduction of depression ($P = 0.002$) and fatigue ($P = 0.02$) and improvement in the synchronization tapping ($P < 0.05$)

[1]Subjects expressing a clear preference for treatment (25% of total) were allocated to music therapy while all others were randomly assigned to either treatment or control group; [2]The goal of random assignment was not fully achieved because of the need to have 2-3 subject available at the same time to held group session in the treatment condition; [3]Subjects heard 1 min of music or noise and after were given all assessments while they were continuously exposed to the sound up to the end of the evaluation; [4]Patients were quasi-randomly assigned to groups making sure that the two groups were as close as possible in terms of numerosity and clinical characteristics of participants. 9HPT: Nine-Hole Pegboard Test; FAST: Frenchay Aphasia Screening Test; HADS: Hospital Anxiety and Depression Scale; MBRS: Musical Behaviour Rating Scale; NRS: Neurobehavioural Rating Scale; VAS: Visual Analogue Scale; SIP: Sickness Impact Profile; ROM: Range of Motion; POMS: Profile of Mood State; SS-QOL: Stroke Specific Quality of Life Scale; RBMT: Rivermead Behavioural Memory Test; WMS-R: Wechsler Memory Scale-Revised; BDAE: Boston diagnostic aphasia examination; CERAD: Consortium to Establish a Registry for Alzheimer Disease; BVRT: Benton Visual Retention Test; MBEA: Montreal Battery of Evaluation of Amusia; FAB: Frontal Assessment Battery; POMS: Profile of Mood State; SAQUOL-39: Stroke and Aphasia Quality of Life Scale-39; BAI: Beck anxiety inventory; BDI: Beck Depression Inventory; ROM: Range of Motion; K-MBI: Korean-Modified Barthel Index; K-POMS-B: Korea-Modified Profile of Mood States-Brief; CES-D: Center for Epidemiologic Studies Depression Scale; HR: Heart Rate; GSR: Galvanic Skin Response; SCT: Star Cancellation Test; LBT: Line Bisection Test; PST: Picture Scanning Test; POMS: Profile of Mood State.

brain, the whole emotional, motivational, and affective state of the person will be altered[88,89].

Table 3 Characteristics of the included studies concerning effects on other neurological disorders

Ref.	Design/ (Jadad)	Subjects (*n*)	Diagnosis	Intervention	Professionals	Frequency	Outcomes measures	Results
Pacchetti *et al*[80]	RCT (2)	32	Parkinson's Disease	Relaxing music, choral singing, breathing/voice exercises, rhythmic movements, collective improvisation, body expression to music. Control group underwent specific motor exercises	Music therapist	Once a week for 3 mo for 2 h,	HM, MS, PDQL, UPDRS	Improvement in emotional ($P < 0.0001$) and motor ($P < 0.034$) functions, activities of daily living, and quality of life ($P < 0.0001$)
Schmid *et al*[81]	RCT (0)	20	Multiple Sclerosis	Active role of both patient and music therapist on playing instruments or singing (Nordoff-Robbins approach)	Music therapist	3 blocks of individual sessions (8 to 10 sessions per block) over the course of 1 yr	BDI, HADS, SESA, HAQUAMS, MSFC	Not significant differences between groups but medium effect size on depression ($d = 0.63$), self esteem ($d = 0.54$), and anxiety ($d = 0.63$)
Thaut *et al*[82]	CCT (0)	54	Acquired brain dysfunctions	Group improvisation, singing, synchronization, attention, and memory exercises with music (Neurologic Music Therapy). Control group spent an equal amount of time resting	Music therapist	4 group sessions on different days for 30 min each	WAIS-III, AVLT, TMT-B, BSI-18, MAACL, SEQ	Improvements on depression ($P = 0.02$), anxiety ($P = 0.04$), sensation seeking ($P < 0.01$), and executive functions (mental flexibility) ($P < 0.01$)
Horne-Thompson *et al*[83]	CCT	21	ALS/Motor neuron disease	Music relaxation, playing/ singing familiar songs, and music and imagery. A second group received a listening intervention of self-selected music while a third control group underwent activities such as reading or watching TV	Music therapist	3 d per week for 30 min each condition	HADS, ESAS, HR, oxygen saturation levels	No effect was found on depression, anxiety, heart rate, and oxygenation levels between groups
Tamplin *et al*[84]	RCT (3)	24	Chronic Quadriplegia	Oral motor and respiratory exercises and therapeutic singing (Neurologic Music Therapy). Control group received group music appreciation and relaxation	Not specified	3 times weekly for 12 wk for 1 h	Standard respiratory function testing, EMG, PVP, POMS, AQoL	Both groups improved in mood ($P = 0.002$). The singing group showed positive effects on arousal ($P = 0.006$), speech intensity ($P = 0.028$), and maximum phonation length ($P = 0.007$)

HM: Happiness Measure; MS; Motor Subscale; PDQL: Parkinson's Disease Quality of Life Questionnaire; UPDRS: Unified Parkinson's Disease Rating Scale; BDI: Beck Depression Inventory; HADS: Hospital Anxiety and Depression Scale; SESA: Self-Acceptance Scale; HAQUAMS: Hamburg Quality of Life Questionnaire in Multiple Sclerosis; MSFC: Multiple Sclerosis Functional Composite; WAIS-III: Wechsler Adult Intelligence Scale-III; AVLT: Auditory Verbal Learning Test; TMT-B: Trial Making Test Part B; BSI-18: Brief Symptoms Inventory-18; MAACL: Multiple Affect Adjective Check List; SEQ: Self Efficacy Questionnaire; HADS: Hospital Anxiety and Depression Scale; ESAS: Edmonton Symptom Assessment System; HR: Heart Rate; EMG: Electromyogram; PVP: Perceptual Voice Profile; POMS: Profile of Mood State; AQoL: Assessment of Quality of Life.

External causal factors related to the environment may promote and characterize those behavioral disorders that are commonly counted accordingly to a bio-psychosocial model and interfere with the cognitive and emotional state of the person thus inducing an important change in the quality of the inter-individual relationships. These disorders may be considered as a reaction to the physical disability and the psycho-social difficulties produced by the disease but also as an adjustment disorder if we consider the impact of the diagnosis on patient's life, or the weight of a chronic illness and all the other factors that may affect patient's quality of life[90-92].

Depressive syndromes in chronic neurological illness are common and disabling. Their etiology is complex and may be multifactorial. Good history taking and detailed examination of physical and mental state (including cognitive function) will usually reveal the diagnosis and the formulation.

Providing a correct diagnosis of an emotional disorder and starting an appropriate treatment may help physicians to increases in function and quality of life of their neurological patients[93].

The current review showed how MT and musical interventions can improve mood and psychological well-being in neurological patients. These clinical results are in accordance with the literature that highlights the effects that music listening and music making have on brain structures of emotion regulation[36], on various neurochemical systems[38], and on neural plasticity[94,95]. However, the strength of this review's findings is limited due to a generally poor methodological quality of the studies and the restricted size of samples. Moreover, the heterogeneity of the outcomes prevented any meta-

analysis. Notwithstanding, the analysis of the 25 RCTs or CCTs included in this work points out a positive effect of interventions with music on psychosocial outcomes such as mood, depression, and quality of life when compared to standard care or other treatments.

CONCLUSION

Music-based activities can represent a valid and without side effects intervention for reducing psychological and behavioral disturbances related to neurological disorders and also for promoting the functional recovery. Specifically, the most significant results of the music interventions on the psychological side can be identified in the aspects more closely related to mood, especially in the reduction of the depressive and anxiety's component, and in the improvement of the emotional expression, communication and interpersonal skills, self esteem and quality of life. As revealed in advance, the efficacy of music and MT interventions could be explained by different points of view. From the neurochemistry point of view we know that music can activate limbic and paralimbic structures, such as the amygdala, the hippocampus, the nucleus accumbens, etc. that function abnormally in patients with a high depressive component. At the psychological level music can engage several social functions, can increase communication and social cohesion and can promote empathetic relationships, especially in the active MT approaches. Finally, from the rehabilitative point of view, making music can involve and influence motor areas functioning and regulation. This effect appears to be connected to the pleasure and thereby can positively affect the mood and consequently the rehabilitative process[36-38].

In conclusion, a more methodological rigor and a clearer definition of music approaches are needed to improve the quality of MT research and to focus on the specific role of music-based interventions in psychological symptoms in the field of neurology.

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REVIEW

Sensation/novelty seeking in psychotic disorders: A review of the literature

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Abstract

The evaluation of personality traits is important for the better understanding of the person suffering from psychosis and for treatment individualization. However literature on patients' personality and character in such disorders is limited. The aim of this review was to summarize the literature on sensation/novelty seeking (SNS), a trait which is biologically based and highly heritable and is associated with dopamine activity, and refers to a person's tendency to seek varied, novel, complex, and intense sensations and experiences. A total of 38 studies were included in this review, involving 2808 patients and 2039 healthy controls. There is consistent evidence that this trait is independently associated with alcohol and substance abuse in patients with schizophrenia and related disorders. The estimation of SNS would help clinicians to identify patients at risk for abuse. There is also some evidence that higher SNS levels may relate to medication non-adherence and seem to increase the risk of patients' aggressive and violent behavior, but studies are scarce. SNS was found not to be related to suicidality, whereas in the fields of patients' quality of life and psychopathology results are contradictory, but most studies show no possible association. Several studies suggest that SNS is lower in psychotic patients compared to controls, whereas most yield no differences. The evidence for this trait as a potential endophenotype of schizophrenia is weak. SNS may be implicated in psychotic disorders' course and prognosis in several ways and should be always inquired for. This trait can be reliably measured with the use of easily applicable self-rated instruments, and patients' accounts could inform clinicians when planning management and delivering individualized treatment.

Key words: Novelty seeking; Personality; Psychosis; Sensation seeking; Schizophrenia; Substance abuse

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Core tip: This review summarizes current research on the personality trait sensation/novelty seeking (SNS) in psychotic disorders. There is an emerging literature on SNS in psychotic patients, suggesting that this trait is associated with patients' alcohol and substance misuse. Some evidence suggests that SNS may be related to medication non-adherence and aggressive behavior, whereas data on other illness dimensions, such as quality of life and psychopathology are scarce and controversial. In general, patients with psychotic disorders appear to have lower SNS levels than healthy controls, but abusing patients, who probably have high SNS levels are often excluded from research.

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INTRODUCTION

Research on schizophrenia and related syndromes has been focused on the study of psychopathology, and the investigation of neurobiology and genetics of these debilitating disorders. Numerous previous and more recent publications address these important issues in psychotic disorders. Biological and psychosocial treatments and treatment delivery has also been the objective of many studies. Literature on patients' personality and character in such disorders is far more limited. However, the evaluation of personality traits is important for the better understanding of the person suffering from psychosis and for treatment individualization. Clinicians should always take into account patients' personality, as proposed by scholars in major educational psychiatric texts[1].

At recent years an increasing number of studies have been edited for the investigation of personality traits of psychotic patients and the effect of personality on the development and expression of symptomatology[2], relapse[3], social functioning[4] and outcome[5].

The concept of the personality trait called "sensation seeking" (SS) has been originally introduced by Zuckerman[6] who defined it as a person's tendency to seek varied, novel, complex, and intense sensations and experiences, and the willingness to take physical, social, legal, and financial risks for the sake of such an experience. Cloninger[7,8] used the term "novelty seeking" (NS) to describe a similar to SS concept in his temperament and character model. Previous and more recent studies support that these two concepts are identical[9,10]. The correlation of SS to NS was found to be as high as 0.68 in the study edited by Zuckerman and Cloninger[9]. Both investigators suggested sensation/novelty seeking (SNS) to be biologically based and highly heritable, and several studies support this notion[11,12]. Moreover, the association of SNS with genes such as DRD4 and COMT, which regulate dopamine activity and are implicated in the pathogenesis of psychotic disorders, has been shown by researchers[13,14]. It seems that SNS is mediated by pathophysiological mechanisms at the neurotransmitter level, and may be particular relevant in psychotic disorders, because dopamine and other neurotransmitters are involved in psychotic symptomatology. It should be noted that concepts related to SNS exist in other personality models, such as the Openness to experiences in the Costa and McCrae's big five personality model[15].

SNS can be reliably measured with the use of instruments such as the Sensation Seeking Scale[16] or as one of the traits included in the Tridimensional Personality Questionnaire (TPQ)[17], or the more recent Temperament and Character Inventory (TCI)[18] which were developed by the researchers. SNS has been studied in healthy persons and mental patients and was found to be associated with alcohol/substance abuse[19,20], in patient populations and risky behavior in healthy subjects[21]. The evidence for the impact of this trait in psychosis is limited. The aim of the present report is to review the literature on SNS in psychotic patients and to stress its clinical relevance.

SEARCH REFERENCES

A search in the database of PubMed was conducted, for English-language articles published up to August 2014, with the combination of each of the search terms "sensation seeking", "novelty seeking", with each of the terms "schizophrenia" and "psychosis". Additional search used the scales names (Sensation Seeking Scale, Tridimensional Personality Questionnaire, Temperament and Character Inventory) in combination with the terms "schizophrenia" and "psychosis". References cited in the originally retrieved publications were searched to identify additional potentially relevant studies. Only studies in which a standardized and valid tool was used for personality traits' evaluation were included in the review. Regarding diagnosis this review comprised studies on patients with schizophrenia and related psychoses. No limits were set in the number of participants in the studies to be included in this review. All studies in which the levels of SNS in psychotic patients were assessed with the use of a valid instrument were included, regardless the study objective and outcome (psychopathology, alcohol/substance abuse, quality of life, medication adherence, suicidality, violent behavior, and other illness dimensions). Finally, all studies comparing SNS levels between patients and control groups were included.

SENSATION/NOVELTY SEEKING IN PATIENTS WITH PSYCHOTIC DISORDERS

The initial search retrieved 130 articles. Most of them were excluded after reading the abstract. The additional search revealed one more relevant paper. Together with the relevant references a total of 38 studies were included in this review, involving 2808 patients and 2039 healthy controls, and 415 patients' first degree relatives.

Results are presented in Tables 1-7. Each table refers to a different study objective and presents briefly the main findings of studies

SNS and psychopathology

Studies on the possible effect of SNS on the symptomatology in psychotic patients yielded inconsistent results (Table 1). Although SNS levels were correlated to psychotic symptoms[22], poor insight[24] and executive

Table 1 Sensation/novelty seeking and psychopathology

Ref.	*n*	Trait-instrument	Main findings
Guillem *et al*[22]	52 schizophrenia outpatients 25 healthy subjects Alcohol/drug abuse was an exclusion criterion for controls	NS, TCI	Positive correlation between NS and the psychotic symptom dimension; lower NS scores in patients compared to controls
Boeker *et al*[23]	22 schizophrenia inpatients 22 healthy controls History of alcohol/drug abuse was an exclusion criterion	NS, TCI	NS was found not to be related to psychopathology. No differences in patients and controls
Ritsner *et al*[24]	107 schizophrenia outpatients Substance abuse was an exclusion criterion	NS, TPQ	Increased NS was associated with poor insight
Guillem *et al*[25]	44 male schizophrenia outpatients 22 healthy controls Alcohol/substance abuse was an exclusion criterion in both groups	NS, TCI	Higher NS levels in patients affected executive function; patients scored lower than controls on NS
Cortés *et al*[26]	47 inpatients with schizophrenia or other non-organic psychoses 47 relatives 188 controls	NS, TCI-R	NS was found not to be related to psychopathology. Moderate difference in patients and controls
Poustka *et al*[27]	41 outpatients with schizophrenia and related psychoses	NS, TCI	Several traits but not NS were found to be related to symptomatology
Song *et al*[28]	33 first-episode schizophrenia patients 50 ultra high risk subjects 120 healthy controls	NS, TCI	NS was not correlated to symptomatology; there were no significant difference in NS between groups

NS: Novelty seeking; TPQ: Tridimensional personality questionnaire; TCI: Temperament and character inventory; TCI-R: TCI revised.

Table 2 Sensation/novelty seeking and alcohol/substance abuse

Ref.	*n*	Trait-instrument	Main findings
Van Ammers *et al*[29]	28 male schizophrenia patients, attending residential and outpatient rehabilitation programs	NS, TPQ	Significant correlation of NS with a history of alcohol/cannabis abuse
Liraud *et al*[30]	45 non-affective psychotic inpatients 58 inpatients with mood disorders	SS, SSS	High SS was associated with increased risk of substance abuse
Dervaux *et al*[31]	100 inpatients and outpatients with schizophrenia or schizoaffective disorder, 41 with a lifetime history of alcohol/substance abuse	SS, SSS	Higher levels of SS were associated with substance abuse
Kim *et al*[32]	102 male schizophrenia outpatients 51 abusing	NS, TCI	Dual-diagnosis patients showed greater novelty seeking
Bizzarri *et al*[33]	47 abusing patients 61 non-abusing patients with schizophrenia spectrum or bipolar disorder or psychotic depression	SS, SCI-SUBS	Abusing patients had higher SS scores
Dervaux *et al*[34]	46 male abusing schizophrenia patients 64 male non-abusing patients	SS, SSS	Higher SS scores in the abusing group
Dervaux *et al*[35]	34 abusing schizophrenia patients 66 non-abusing patients	SS, SSS	Higher mean scores on SS in patients with a lifetime history of abuse
Zhornitsky *et al*[36]	31 abusing schizophrenia patients 39 patients with substance abuse 23 non-abusing schizophrenia patients 25 healthy controls	SS, SSS	SS total score was significantly higher in abusing patients, irrespectively of the diagnosis of schizophrenia

SS: Sensation seeking; NS: Novelty seeking; SSS: Sensation Seeking scale; TPQ: Tridimensional personality questionnaire; TCI: Temperament and character inventory; SCI-SUBS: Structured clinical interview for the spectrum of substance use.

function[25] in different studies, these results were not replicated by subsequent reports. Importantly, in most studies there was no association between SNS and symptoms' expression.

SNS and alcohol/substance abuse

The role of SNS in psychotic patients' alcohol/substance abuse has been a field of extensive investigation (Table 2), including the first study on SNS in schizophrenia patients[29]. Eight studies have examined SNS in abusing patients and they consistently reported that this trait is associated with alcohol/substance abuse. Notably, 3 studies are restricted to male patients[29,32,34]. Interestingly, in the most recent study in the field, abusing subjects with and without schizophrenia had higher SS levels compared to non-abusing schizophrenia

Table 3 Sensation/novelty seeking and quality of life

Ref.	*n*	Trait-instrument	Main findings
Hansson *et al*[37]	104 outpatients with schizophrenia, schizophreniform disorder, or schizoaffective disorder	NS, TCI	Several personality dimensions, but not NS were correlated to subjective quality of life
Ritsner *et al*[38]	90 inpatients and outpatients with schizophrenia Drug/alcohol abuse was an exclusion criterion	NS, TPQ	Higher levels of NS were associated with better general quality of life
Kurs *et al*[39]	47 schizophrenia outpatients, 47 non-affected siblings 56 healthy subjects Drug/alcohol abuse was an exclusion criterion	NS, TPQ	Harm avoidance but not NS was associated with general quality of life. There were no differences in NS between patients, siblings and controls
Margetić *et al*[40]	120 schizophrenia outpatients 120 first degree relatives 129 healthy controls History of drug/alcohol dependence was an exclusion criterion	NS, TCI	Quality of life was not related to NS. Patients scored lower on NS compared to controls, and similar to relatives
Jetha *et al*[41]	41 outpatients with schizophrenia spectrum disorders 41 healthy controls	NS, TCI	NS was not related to any aspect of quality of life. Patients had significantly lower scores on NS than controls

NS: Novelty seeking; TPQ: Tridimensional personality questionnaire; TCI: Temperament and character inventory.

Table 4 Sensation/novelty seeking and medication adherence

Ref.	*n*	Trait-instrument	Main findings
Liraud *et al*[42]	45 inpatients with schizophrenia and related psychoses 58 inpatients with mood disorders	SS, SSS	SS was associated with poor medication adherence
Aukst Margetić *et al*[43]	76 schizophrenia outpatients Substance abuse was an exclusion criterion	NS, TCI	NS was associated with medication non-adherence

SS: Sensation seeking; NS: Novelty seeking; SSS: Sensation Seeking scale; TCI: Temperament and character inventory.

Table 5 Sensation/novelty seeking and suicidality

Ref.	*n*	Trait-instrument	Main findings
Albayrak *et al*[44]	94 schizophrenia outpatients, 46 attempters History of drug/alcohol dependence was an exclusion criterion	NS, TCI	No association of NS with suicide attempts
Aukst Margetić *et al*[45]	120 schizophrenia outpatients, 29 with attempted suicide History of drug/alcohol dependence was an exclusion criterion	NS, TCI	No association of NS with suicidality and suicide attempts

NS: Novelty seeking; TCI: Temperament and character inventory.

patients and healthy controls[36].

SNS and quality of life/social functioning

Five studies (Table 3) have addressed the possible effect of SNS in subjective quality of life in schizophrenia patients. With one exception, results are consistent in that SNS is not associated with quality of life in patients' population, in contrast with other traits, such as harm avoidance. Only the study of Ritsner *et al*[38] showed that higher NS levels were associated with better general quality of life.

SNS and treatment adherence

Only two studies (Table 4) were conducted with the objective to assess the impact of SNS on medication adherence, involving in-and outpatients. Higher SNS scores were associated with poor medication adherence in patients, independently from a history of substance abuse in one study[42], whereas in the other[43] substance abuse was an exclusion criterion.

SNS and suicidality

Two studies on the effect of personality on suicidality in schizophrenia patients reported consistently no association of SNS with previous suicide attempts (Table 5). Notably, in both studies current or past history of alcohol/substance abuse was an exclusion criterion.

SNS in other aspects of psychotic disorders

One study[46] yielded no association of SNS with patients' disability; SNS was found also not to be related to coping and recovery style in psychotic disorders in another report[48]. Two studies[47,49] addressed the

Table 6 Sensation/novelty seeking and other illness dimensions

Ref.	*n*	Trait-instrument	Objective	Main findings
Herrán *et al*[46]	62 schizophrenia outpatients, 43 healthy subjects	NS, TPQ	Disability	Several personality traits, but not NS were associated with disability. There were no differences in NS between patients and controls
Fresán *et al*[47]	102 schizophrenia outpatients (61 violent) Current (the last 4 mo) alcohol/substance abuse was an exclusion criterion	NS, TCI	Aggressive/violent behavior	NS was a risk factor for violent behavior
Modestin *et al*[48]	64 inpatients with schizophrenia spectrum disorders	NS, TPQ	Coping/recovery style in psychotic illness	No association with NS
Lejoyeux *et al*[49]	100 schizophrenia inpatients	SS, SSS	Aggressive/violent behavior	SS was not associated with patients' aggressive behavior. Sub-scores on SSS were correlated to the OAS scores

SS: Sensation seeking; NS: Novelty seeking; SSS: Sensation Seeking scale; TPQ: Tridimensional personality questionnaire; TCI: Temperament and character inventory; OAS: Overt Aggression scale.

Table 7 Sensation/novelty seeking in psychotic patients and control groups

Ref.	*n*	Trait-instrument	Main findings
Szöke *et al*[50]	45 schizophrenia inpatients 126 controls	NS, TPQ	No differences in NS between groups
Ritsner *et al*[51]	90 schizophrenia outpatients 136 controls Drug/alcohol abuse was an exclusion criterion	NS, TPQ	No differences in NS between groups
Calvó de Padilla *et al*[52]	11 chronic untreated schizophrenia patients 11 first-degree relatives 12 controls	NS, TCI	No differences in NS between groups
Farhady *et al*[53]	69 schizophrenia inpatients 50 healthy controls	SS, SSS	Lower SS in patients
Hori *et al*[54]	86 schizophrenia patients 115 healthy controls Substance abuse during the past 6 mo was an exclusion criterion	NS, TCI	Lower NS in patients
Smith *et al*[55]	35 schizophrenia in- and outpatients 34 non-psychotic siblings 63 controls 56 controls' siblings Current substance abuse was an exclusion criterion	NS, TCI	No differences in NS between groups. No association of NS with psychopathology dimensions
Gonzalez-Torres *et al*[56]	61 inpatients with schizophrenia or schizophrenia spectrum disorders 59 first degree relatives 64 healthy controls Substance abuse was an exclusion criterion	NS, TCI	NS scores were not different in patients and controls; patients scored higher on NS than relatives
Ohi *et al*[57]	99 schizophrenia patients 179 controls Substance-related disorders were an exclusion criterion for patients	NS, TCI	Lower NS in patients
Sim *et al*[58]	48 patients with schizophrenia or schizoaffective disorder 97 first-degree relatives 106 controls History of substance use was an exclusion criterion	NS, TCI	No differences in NS between groups
Miralles *et al*[59]	161 schizophrenia inpatients, 214 healthy controls	NS, TCI-R	No differences in NS between groups; in males the number of psychiatric admissions positively correlated with NS
Hori *et al*[60]	106 schizophrenia outpatients 247 healthy controls Substance use was an exclusion criterion for controls	NS, TCI	NS was found to be significantly lower in symptomatic (n = 72) but not in remitted patients

NS: Novelty seeking; TPQ: Tridimensional personality questionnaire; TCI: Temperament and character inventory; TCI-R: TCI revised; SSS: Sensation Seeking scale; SS: Sensation seeking.

possible association of violent behavior of patients with schizophrenia with SNS. Both found that higher SNS levels were correlated with higher scores on the Overt Aggression Scale (OAS), but in the study of Lejoyeux *et al*[49] SS did not appear in the logistic regression to be a risk factor for aggressive behavior (Table 6).

SNS levels in psychotic patients and controls

As appears in Table 7 there are 10 studies on the estimation of SNS levels in psychotic patients. Additionally there are 9 studies described in other tables (see Tables 1, 3 and 6) in which SNS levels on patients and healthy controls where examined among other objectives. Overall results are inconclusive. Seven studies (see Tables 1, 3 and 7) suggest that SNS levels are lower in psychotic patients, whereas in most (11 studies, see Tables 1, 3, 6 and 7) no difference is observed. Interestingly, in one of the most recent studies[60] NS was found to be significantly lower in symptomatic but not in remitted patients. Recently Ohi *et al*[57] performed a case-control study and a meta-analysis comprising seven studies to estimate personality differences between patients and healthy controls. Regarding NS, they found no overall differences in scores between patients and controls. However, there was evidence of heterogeneity among studies for NS, and in the subgroup analysis the effect size for this trait was affected by study location. Asian populations presented significant difference between patients and controls, whereas in European populations there was no difference in NS between patients and controls, suggesting a possible cross-cultural difference.

DISCUSSION

This review extends the findings of two previously published meta-analyses[57,61], in which only studies using the TPQ/TCI were included, on the impact of the SNS trait on psychotic disorders. Here, a total of 38 studies are included referring to the similar concepts of SS and NS in psychotic patients. There is an emerging literature on the personality trait SNS in psychotic patients. There is consistent evidence that this trait is independently associated with alcohol and substance abuse in patients with schizophrenia and related disorders. These results are in line with research on abusing subjects without a comorbid psychotic disorder[62]. It seems that SNS increases the risk of substance abuse in psychotic patients as in other populations. Importantly psychotic patients demonstrate high abuse rates and abuse is associated with poor prognosis[63]. It may be clinically relevant to inquire for SNS in psychotic patients, particularly first episode patients as it might have a predictive value in identifying those who may be prone to abuse. Accordingly, this may determine the implementation of specific interventions.

There is also some evidence for the impact of SNS on other important aspects of psychosis, such as treatment adherence and violence. Higher SNS levels have been related to medication non-adherence and seem to increase the risk of patients' aggressive and violent behavior, but studies are scarce. Taken together these findings suggest that SNS may affect psychotic disorders' course and prognosis in several ways. For instance, inadequate medication adherence and a history of substance abuse are both predictive of an unfavorable outcome. This is in line with previous evidence regarding personality traits such as neuroticism[5], which suggests that personality dimensions are associated with psychotic disorders' outcome.

Personality traits including SNS have been also studied in psychotic patients who have attempted suicide. Suicidality is not uncommon in schizophrenia, and up to 5% of patients complete suicide[64]. Two studies have addressed this issue, and found that SNS levels were not related to suicidality[44,45]. Notably, in both studies current or past history of alcohol/substance abuse was an exclusion criterion. This could have bias the results in that the excluded abusing patients would be expected to have higher SNS levels. More recently, suicide attempts were examined as one of the objectives of the study of Miralles *et al*[59], described in Table 7. Similarly to the aforementioned reports, no correlation of SNS with the number of suicide attempts was found, but importantly in this study, patients with a history of alcohol/substance abuse were not excluded. These results are in line with previous research which suggested that NS scores were not correlated with suicide attempts in psychiatric in-patients with several non-psychotic disorders[65].

Regarding the impact of SNS on psychopathology, most studies[23,26-28] revealed no association. Some research however has inconsistently suggested a correlation with psychotic symptoms, poor insight and executive dysfunction[22,24,25]. These results need replication to determine whether SNS is implicated in the symptomatology of psychotic disorders, and if so what are the exact neurobiologic pathways of such a correlation. Research on the association of SNS with measures of subjective quality of life yielded mixed results, but most studies do not support any correlation. Interestingly, in the study of Miralles *et al*[59] NS was found to be positively correlated with the number of admissions to a psychiatric hospital in male patients.

It is generally believed that schizophrenia patients have a unique personality profile as estimated with the use of different personality models[66]. Regarding studies using Cloninger's temperament and character model several personality dimensions have been found to be altered in schizophrenia[57]. However, it is unclear whether SNS levels differ in psychotic patients as a group, compared to healthy individuals. Some studies (see Tables 1, 3 and 7) suggest that SNS is lower in psychotic patients, whereas most (see Tables 1, 3, 6 and 7) yield no differences. The meta-analysis by Ohi *et al*[57] showed no differences in European populations, but significant lower levels of SNS in Asian subjects. Overall, this trait was not different in patients and controls, but there was heterogeneity among studies. A previous meta-analysis suggested

that the overall level of NS was lower among individuals with schizophrenia compared with controls, but the difference was not statistically significant[61]. It should be noted however that in many studies a history of alcohol and/or substance abuse was an exclusion criterion. Given the high rates of abuse in schizophrenia patients this means that a large proportion of patients who probably had higher SNS levels were excluded from research. Conceivably, this might have biased the results and may explain the reported lower SNS levels in the patient population. It might be argued that schizophrenia patients as a group have SNS levels comparable to healthy persons. It appears that SNS does not increase the risk of schizophrenia and thus it may not be a potential endophenotype of schizophrenia, in contrast to other temperamental components, such as harm avoidance, as supported by several studies involving patients, siblings and other first-degree relatives[54,55,58]. Notably, some researchers have argued that healthy controls participating in research protocols and been recruited *via* advertisements in the media may be those with the higher SNS levels among the healthy population[54]. According to the definition of SNS it is not clear how participating in these procedures would be such an exciting experience for the supposed high SNS individuals. However, if this is the case of research healthy participants, and bearing in mind that in several studies patients with the higher SNS levels (who are more likely to be abusing patients) are excluded, it is an intriguing question whether psychotic patients may in fact have higher levels of SNS than the general population. However, this is not supported by the few studies in which alcohol/substance abuse was not an exclusion criterion (see Tables 1, 6 and 7), and showed patients' SNS levels to be equal or lower[41] than controls'. Evidence from the study of schizophrenia patients with the application of other personality models, such as the Costa and McCrae Five Factor model, also suggests that Openness to experiences levels (a concept close related to SNS) are lower in schizophrenia patients compared with healthy controls[67]. Future research should not exclude dual diagnosis patients to clarify this issue.

From a methodological perspective, it could be argued that all studies have used self-report personality assessments, which are not objective. However, research has shown that personality domains can be reliably measured with self-report instruments and results are easy to obtain[57,68], which renders such assessments relevant for clinical use.

This study has some limitations. The search was limited only to a single database (PubMed) and this may mean that several relevant studies included in other databases may have been missed. Another limitation is that the search was restricted to English-language articles, and studies in other languages were omitted.

CONCLUSION

Although personality traits may not be easily amenable to modification, it is important for clinicians to acknowledge and take into account such patients' characteristics when planning and releasing treatment formulations. The evaluation of SNS may thus be an important part of clinical examination, and should be routinely performed. This trait can be reliably measured with the use of easily applicable self-rated instruments, and patients' accounts could inform clinical practice and should be taken into account by clinicians when planning management and delivering individualized treatment. It is proposed that practicing clinicians should regularly inquire for SNS when assessing patients' personality as integrated part of the diagnostic workup. The clinical relevance of exploring SNS trait in subjects with severe psychiatric disorders is that it would help to identify patients prone to substance abuse or to medication non-adherence and perhaps violent behavior. This would facilitate the implementation of trait-specific interventions, when available.

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REVIEW

Transcranial direct current stimulation in psychiatric disorders

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Abstract

The interest in non-invasive brain stimulation techniques is increasing in recent years. Among these techniques, transcranial direct current stimulation (tDCS) has been the subject of great interest among researchers because of its easiness to use, low cost, benign profile of side effects and encouraging results of research in the field. This interest has generated several studies and randomized clinical trials, particularly in psychiatry. In this review, we provide a summary of the development of the technique and its mechanism of action as well as a review of the methodological aspects of randomized clinical trials in psychiatry, including studies in affective disorders, schizophrenia, obsessive compulsive disorder, child psychiatry and substance use disorder. Finally,

we provide an overview of tDCS use in cognitive enhancement as well as a discussion regarding its clinical use and regulatory and ethical issues. Although many promising results regarding tDCS efficacy were described, the total number of studies is still low, highlighting the need of further studies aiming to replicate these findings in larger samples as to provide a definite picture regarding tDCS efficacy in psychiatry.

Key words: Non-invasive brain stimulation; Transcranial direct current stimulation; Psychiatry disorders; Review

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Core tip: Transcranial direct current stimulation (tDCS) has been the subject of great interest among researchers because of its easiness to use, low cost, benign profile of side effects and encouraging results of research in the field. In this review, we provide a summary of the development of the technique and its mechanism of action as well as a review of the methodological aspects of randomized clinical trials in psychiatry and we provide an overview of tDCS use in cognitive enhancement as well as a discussion regarding its clinical use and regulatory and ethical issues.

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INTRODUCTION

The interest in the brain stimulation using electricity exists since the Roman Empire, when the physician Scribonius Largus described the application of the electric shocks from "torpedo fish" to relieve headache[1,2]. In recent history, the first report of cortical stimulation occurred in 1802, when Giovanni Aldini described the electrical stimulation of exposed human cortex. He also reported the use of a voltaic pile to perform transcranial electrical stimulation to treat melancholia[2,3]. In fact, the invention of the voltaic battery encouraged the application of electrotherapy for medical purposes and during the 19th and 20th centuries physicians started to use galvanic batteries to perform electric brain stimulation for the treatment of different mental disorders with heterogeneous, dubious results. Notably, these first interventions were largely empirical and uncontrolled. Only in the 1950s and the 1960s systematic research was conducted in animals models, studying the effects of direct current (DC) on changing cortical excitability, and in clinical trials, performing DC stimulation for the treatment of depressive or manic symptoms[2]. The interest on "brain polarization" (as transcranial DC stimulation was described at that time) declined during the 2nd half of the last century, with the social stigma related to electroconvulsotherapy and the "golden age" of psychopharmacology. Only in the last 15 years, the findings that weak, DC stimulation delivered transcranially (tDCS) could induce prolonged neuroplastic changes in cortical excitability[4,5] with functional effects in healthy subjects[6], contributed to a resurgence of the interest in this technique not only as research tool but also as a potential approach for the treatment of several psychiatric disorders, such major depressive disorder, schizophrenia, obsessive-compulsive disorder and also other psychiatric and neurological disorders[7-11].

Technical aspects and mechanisms of action of tDCS

tDCS is described as a non-invasive form of brain stimulation that uses a low-intensity, constant current applied directly to the head through scalp electrodes[12]. This form of brain stimulation can induce significant currents in superficial cortical areas (see The stimulated brain, Elsevier 2014, Chapter 2, for a review and further references) and, since the current used is sub threshold, it can modulate neuronal excitability without triggering action potentials[13], by facilitation or inhibition of spontaneous neural activity according to the polarity of the electrodes[14]. Generally, anodal stimulation induces an increase of cortical excitability, whereas cathodal stimulation decreases cortical excitability, effects that may last beyond the stimulation period[4,5], up to 30-120 min[15]. In fact, the polarity-dependent effects are more complex and also dependent of the spatial organization of the cells: inward current flow at the cortex (anodal tDCS) generates hyperpolarization of apical dendritic regions of pyramidal cortical neurons and depolarization of somatic regions, whereas outward current flow (cathodal tDCS) results in somatic hyperpolarization and apical dendrite depolarization of pyramidal cortical neurons[16].

The effects of tDCS are not only determined by the polarity of the electrodes, but also with the dose[16]. This involves the current intensity (usually ranging between 0.5 to 2 mA)[12], the duration of stimulation (usually ranging between 5 to 40 min)[7] and the size of the electrodes that varies from 3 to 100 cm^2[17]. These variables determine the current density (in A/m^2) and the total charge (in Coulombs) applied. Notwithstanding, the actual current delivered to the cortex is also influenced by several other uncontrollable factors such as the impedance of the cephalic structures[7].

The electrode placement on the scalp is usually determined using the international Electroencephalogram (EEG) 10-20 System[17]. Commonly, the active electrode is placed on the scalp, whereas the reference electrode can be placed on either another cephalic location (bipolar or bicephalic montage) or an extracephalic

location (unipolar or monocephalic montage), usually the shoulder or upper arm. The electric current enters the brain through the anode, passes through the scalp and skull before reaching cortical and subcortical regions and finally leaves through the cathode (The stimulated brain, Elsevier 2014, Chapter 2). The current flow produced reaches deep structures and, when using extracephalic electrodes, the midbrain and spinal cord as well. Importantly, the conventional montages used in tDCS present low precision - *i.e.*, the current flow produced is not restricted to the area under the electrodes but in fact spreads out to other cortical regions between and around the electrodes[18].

The long-term effects of tDCS appear to operate through bidirectional modifications of post-synaptic connections similar to long-term potentiation (LTP) and long-term depression (LTD), occurring through NMDA-depended mechanisms[19]. Indeed, repeated tDCS sessions might further increase the duration of long-term effects on behavioral outcomes[20].

Methodological aspects in clinical tDCS research

Over the past years, tDCS has been increasingly used in clinical research, from basic neuroscience research to a tool in the treatment of various neurologic and psychiatric disorders[21,22]. In order to identify whether the effects of tDCS are non-specific or random, the use of a placebo (sham) group is mandatory in clinical trials. Indeed, the use of placebo is a standard method to blind participants and health care providers in randomized, controlled trials[23]. Within this context, the development of reliable methods of sham stimulation is challenging[24], as blinding failure can compromise evaluations, resulting in biased assessment of intervention effects.

The sham stimulation, method validated by Gandiga and colleagues[25], is currently used in almost all tDCS clinical trials. The procedure involves short-lasting manual or automatic increase and decrease of current delivered during the first moments (30-60 s) of the stimulation session in order to simulate the same skin sensations of the verum stimulation[25-27]. Palm and colleagues[28] reported that using this blinding method the subjects were not able to distinguish between active and sham stimulation applied on prefrontal areas. However, in this study, the investigators were able to identify between active *vs* sham stimulation group based on the skin redness provoked by the active stimulation. In another research, Ambrus and colleagues suggested that this method of blinding is effective, not because the sham fade-out phase mimics the presumed disappearance of the sensations in the verum stimulation conditions, but because, the cutaneous sensations associated with the sham stimulation persist after the ramp-down phase[29].

Another concern of tDCS detection involves current dose, which seems to be associated with active tDCS detection[28] since it is related to immediate adverse effect, especially discomfort sensation. In a randomized double blind crossover trial with 100 healthy volunteers, O'Connell *et al*[30] suggest that blinding in studies using tDCS at intensities of 2 mA is inadequate once the participants correctly judged the stimulation condition.

Furthermore, some authors suggest that longer ramp-in phases are preferable for blinding purposes, especially when daily tDCS sessions are applied[24,31]. In fact, randomized clinical trials (RCTs) tDCS trials, which use parallel designs, might provide a more adequate blinding. In a recent RCT for major depression with a factorial design and two active interventions (sertraline/placebo and 2 mA active/sham tDCS), blinding assessment of the pharmacological and non-pharmacological interventions was comparable, with correctly blinding guessing primarily associated with clinical improvement and adverse effects and not blinding failure[24].

Skin redness and discomfort are common adverse effects that can harm tDCS blinding, and some studies have been performed in order to control them. Guarienti *et al*[32] found that topical pre-treatment with ketoprofen 2% significantly attenuated the tDCS-induced erythema, with a medium effect as compared to placebo. Moreover, the unblinding of this adverse effect can be managed by avoiding the awareness of participants (for instance, looking at the mirror or contacting peers following stimulation) and raters (for instance, by adopting a rest period between tDCS session and the clinical interview). McFadden *et al*[33] reported the reduction of pain and discomfort associated with tDCS by using local anesthetics. A recent report showed that pretreatment with benzocaine 6%, a topical numbing agent, can decrease the discomfort in subjects during the stimulation using high definition (HD) electrode design, which can enhance the efficiency of the sham controlled studies[34].

Adverse effects and safety

The general impression is that tDCS is a safe technique with mild and transient adverse effects (AEs). Human data on safety and tolerability are largely provided from single-session studies in healthy volunteers. In a meta-analysis, Brunoni and colleagues[31] showed that tDCS presents a benign profile of side effects when used in 1-2 sessions for healthy volunteers; however, they referred that only 56% of all reviewed studies reported the presence/absence of AEs, concluding that AEs are being insufficiently reported during tDCS clinical research.

According to this meta-analysis, the most common adverse effects are detected in the active group, among which itching, tingling, headache, burning sensation and discomfort (Table 1).

Although well investigated in adults, there is no specific guidance for tDCS dosage in children. The few studies investigating tDCS among the pediatric population indicated that adverse effects were similar

Table 1 Adverse effects associated with transcranial direct current stimulation

Adverse effects	Active[1]	Sham[1]
Itching	46 (39.3%)	27 (32.9%)
Tingling	26 (22.2%)	15 (18.3%)
Headache	17 (14.8%)	13 (16.2%)
Burning	10 (8.7%)	8 (10%)
Discomfort	12 (10.4%)	11 (13.4%)

[1]Number of subjects reporting adverse symptom (% in the sample). Adapted from Brunoni *et al*[31], 2011. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation.

to adults, restricted to itching or tingling sensations at the stimulation site and without the reporting of any serious side effects[35]. A naturalistic study in 14 children with language disorders showed that 10 sessions of tDCS were well tolerated and the main side effect detected was irritability, followed by acute mood changes, tingling and itching[36].

However, due to anatomical and neurophysiological differences in the developing brain (*i.e.*, skull thickness, cerebrospinal fluid volume, white and gray matter volumes) the dose parameters considered safe and efficacious for the use in adults should be adjusted to achieve comparable results in children[37].

Recently, Kessler *et al*[37] conducted a study in order to evaluate the safety aspects of tDCS in children. Using magnetic resonance imaging (MRI), they derived head individual models by two neurologically normal children and by three adults with different head sizes and circumferences; their analyses showed an overlap of sensitivity between adults with smaller head size and children aged between 8 and 12 years. Moreover, they highlighted to pay of caution in applying current intensities of 2 mA or greater in pediatric populations, due to the fact that the average of the dose of current over the cortical surface after the tDCS stimulation after might be higher in children than adults.

USE OF TDCS IN PSYCHIATRIC DISORDERS

As a neuromodulatory tool, tDCS was reappraised in the turn of the 21st century, with the seminal works of Priori[38], followed by Nitsche *et al*[4]. They showed that the induction of a weak, direct current through electrodes placed over the scalp could increase (anode) and decrease (cathode) cortical excitability beyond the period of stimulation. It is exact mechanisms of action are still being elucidated but it probably operates by inducing small changes (< 1 mV) in the membrane potential[39], thus acting in the frequency of spike timing and modifying net cortical excitability[40]. The mechanisms of action of tDCS occur also at the synaptic level. For instance, glutamate antagonists abolish tDCS after-effects, while NMDA-agonists enhance them[41].

Compared to repetitive transcranial magnetic stimulation (rTMS), tDCS is a relatively cheaper, easier to use, more portable technique with even less adverse effects. Such appealing characteristics motivated the research of using tDCS for the treatment of neuropsychiatric disorders (for a review see[11]), and, among them, tDCS has been showing particularly positive results in major depression.

Major depressive disorder

Major depressive disorder is a severe psychiatric disorder, chronic and prevalent, showing a life prevalence between 6% and 12% and yearly between 3% and 11% in the whole world[42]. Besides that, proximately 80% of the patients present a recrudescence of depressive symptoms after one year of treatment with antidepressant drugs and up to 33% do not achieve complete remission after the use of 2 or 3 medication trials, which characterizes the treatment resistant depression[43]. In view of its complexity and heterogeneity, with variations in it is etiology, symptoms, course and response to the treatment, further investigation aiming to refine the knowledge underlying neurobiology is needed, with the goal to identify circuits and brain areas connected with this pathology.

An important body of evidence coming from neuroimaging studies suggests that depression is a result of impairment in activity of neural circuits that connects the dorsolateral prefrontal cortex (DLPFC) and the limbic system to other subcortical structures[44]. The current neural models of depression propose that the emotional deregulation is due to abnormalities in the dorsal neural system (cognitive control system) and the ventral neural system (emotional evaluation system)[45]. The dorsal system, which comprehends the DLPFC, dorsomedial PFC, the anterior dorsal cingulate gyrus and the hippocampus, is involved both in the cognitive processing of emotional input as much as the voluntary regulation of emotion. The ventral system, which comprehends the amygdala, insula, the ventral striate, dorsal cingulate gyrus and ventral PFC is critic for the identification of the emotional meaning from both internal or external stimuli, for the automatic generation and regulation (regulation without any conscious effort) of affective states, mediation of automatic response, dependent of the stimuli and context that results in the production of the affective states. It was proposed that increase of ventral neural system activity and decrease of the dorsal neural system activity can result mainly in attention impairment, in the identification of negative emotions and in other cognitive and vegetative symptoms of the depressive disorder[46].

tDCS in the major depressive disorder

In depression, the rationale of the montage with the anode positioned over the left DLPFC and the cathode over the right DLPFC, the right supraorbital area or in

an extra-cephalic position[7] rests on: (1) the prefrontal asymmetry theory of depression, with relative hypoactivity over the left and relative hyperactivity over the right[47,48]; (2) the improvement in working memory and affective processing observed after one-single tDCS session in depressed patients[49-51]; (3) the top-down, neuromodulatory effects of tDCS, possibly reversing the imbalance between hypoactive cortical areas and hyperactive subcortical areas[48]; and (4) the clinical effects observed in rTMS using either rapid, facilitatory stimulation over the left DLPFC and slow, inhibitory stimulation over the right DLPFC[52,53].

In the beginning of this century, some RCTs investigating the efficacy of tDCS for treating depression have showed promising results. Fregni *et al*[54] (n = 10, tDCS given at 1 mA, 20 min per session, 5 sessions on alternate days) and Boggio *et al*[55] (n = 40, 2 mA, 20 min, 10 sessions on consecutive weekdays) both found tDCS more effective than a sham control. Negative results were found in the study conducted by Loo *et al*[56] (n = 40, 1 mA, 20 min, 5 sessions on alternate days followed by 5 further active treatments) clinically meaningful improvement was seen with active tDCS over 10 sessions of treatment, but differences failed to reach statistical significance over the initial 5-session sham-controlled comparison period.

Although a variety of studies have found promising results in the reduction of depressive symptoms treated with tDCS protocols, two recent meta-analyses found different results. While Kalu *et al*[57] conducted a meta-analysis that found improvement in the depressive symptoms in the active group compared with the sham tDCS group, Berlim *et al*[58] did not find significant differences in the rates of response between the active and the sham treated groups, although it is important to emphasize that those meta-analyses considered distinct outcomes. Kalu *et al*[57] considered the size of the effect based on the depression classification scores while Berlim *et al*[58] focused on the rates of remission and response. Some reasons for these mixed findings include relatively small sample sizes, disparate treatment modalities (including number of sessions, cathode positioning, duration and intensity of the sessions, *etc.*) and different depression characteristics (regarding refractoriness, severity, mean age, unipolar *vs* bipolar depression and concomitant use of pharmacotherapy) in the sample. In fact, a more recent meta-analysis[8] found that active *vs* sham tDCS had greater efficacy considering depression improvement as well as response and remission rates.

The largest controlled study so far about the application of tDCS in depression was recently published by Brunoni *et al*[59]. The authors made a controlled trial with 120 patients with depression. The results of this factorial study in which patients were randomly assigned to receive active tDCS/sham tDCS and verum sertraline/placebo showed a significant improvement on the depressive symptoms for the ones that took only active tDCS or in combination with sertraline.

Nonetheless, further randomized clinical trials are necessary and, in fact, several trials evaluating the clinical efficacy of tDCS in depression are being currently performed worldwide. Therefore, in the next years a definite answer regarding the role of tDCS in the therapeutic arsenal of depression is expected.

Bipolar disorder

The etiopathogenic and physiopathological mechanisms of bipolar depression are not yet completely known. One important factor, however, seems to be the "hereditary-genetic". While the general risk to develop the bipolar disorder in the general population is between 1% and 2%, it goes up to 9% in first degree relatives of a Bipolar "carrier". The conformity between homozygous twins varies between 40% and 50% and the heritability (proportion of disease risk in the population due to genetic variation) can reach 80%-85%[60].

From the neuroimaging point of view, several studies indicate the commitment of some structures involved in the affective regulation, such as PFC, anterior cingulate gyrus and amygdala. Neurophysiologic studies in bipolar patients, in turn, indicate executive and attention deficits, corroborating the idea of a commitment of the PFC[61].

TDCS in bipolar depression

A recent study enrolling 31 patients (14 with bipolar depression and 17 with unipolar depression) had all the subjects submitted to a specific protocol: 5 sessions of tDCS with 20 min each, using anodic stimulation over the left DLPFC. The treatment was well tolerated by all and no significant adverse effects were observed. After the fifth tDCS session, depressive symptoms decreased in both groups and the beneficial effects lasted for a month[62].

Loo *et al*[63], in which eight patients with bipolar depression (four in each group) were recruited, did not show important results in RCT phase, however on follow up approach the outcomes were more expressive. Thus, new studies are needed to reinforce the rationale of use in order to validate this technique in this illness.

Schizophrenia

Schizophrenia is a mental disorder that occurs in 0.5%-1.5% of the population[64]. The clinical symptomatology of the disorder can be divided in three groups of symptoms: positive, negative and cognitive. The positive symptoms are characterized by hallucinations, delusions, thought disorders and movement disorders. Negative symptoms involve blunted affect, lethargy, and social withdrawal. Traditional antipsychotic medications have limited efficacy in treating these chronic, often refractory, symptoms[65]. It is appraised that patients treated with antipsychotics remit in 30% of cases, respond partially in 30% and do not respond in about 40%[66]. The best pharmacological option is clozapine, which is the first-line drug for patients with treatment-resistant schizophrenia, defined as the failure

of two adequate antipsychotic trials[67]. About 30% of patients treated with clozapine responds partially and these cases are described as super-refractory[67]. These patients are treated of different ways. Even if the evidence regarding non- pharmacological therapies is still limited, a recent meta-analyses have shown promising results in the application of rTMS in the treatment of auditory verbal hallucinations and negative symptoms[68,69]. Neuroimaging studies have highlighted that these symptoms might be linked to abnormal brain activities within large dysfunctional brain networks. Auditory verbal hallucinations have been linked to fronto-temporal abnormalities with an hyperactivity in the left temporo-parietal junction[70] and negative symptoms have been linked to hypoactivity in the right and left prefrontal cortex[71].

Thanks to the excitatory effect of the anode and the inhibitory effect of the cathode described in the neurophysiological studies investigating the effect of tDCS on motor cortex excitability, it has been hypothesized that anodal tDCS applied over the left prefrontal cortex (hypoactive) combined with cathodal tDCS applied over the left temporo-parietal junction (hyperactive) could alleviate auditory hallucinations in patients with schizophrenia (for a review see Mondino[72]). In the same way, bifrontal tDCS with the anode placed over the left prefrontal region and the cathode over its right homologue or the right supraorbital region is assumed to decrease negative symptoms. Based on these hypotheses, several studies have investigated the clinical effects of tDCS in these two indications in schizophrenia. Current was set at an intensity of 2 mA and delivered during 20 min. The electrodes were placed over the scalp of the subjects according to the 10/20 EEG international system. The center of the electrode was placed on a point situated midway between T3 and P3 to stimulate the left temporo-parietal junction and on F3 (F4) or between F3 and FP1 (F4 and FP2) to stimulate the left (right) prefrontal region.

Another study evaluated 20 patients with predominant negative symptoms and stable medication (> 3 wk) and they were randomized to active or sham stimulation groups[73]. Anode was placed over the left DLPFC and cathode over the right supraorbital area; tDCS was delivered once a day for 10 d. The active group showed significant amelioration in The Positive and Negative Syndrome Scale two weeks after the end of stimulation.

Regarding bifrontal tDCS, only some case-studies have highlighted the potential interest of tDCS to reduce resistant negative symptoms[74,75] and catatonic symptoms[76].

Regarding safety, on the total amount reported in world literature of about 50 schizophrenic patients that have received tDCS, the technique appears to be remarkable safe in the short and medium-terms[77]. Regarding adverse effects, some reviews described only mild adverse effects associated to tDCS such as tingling, itching and fatigue, similarly as observed in literature[78,79].

Of note, two recent case studies have reported the clinical interest of original stimulation parameters using transcranial random noise stimulation. This kind of stimulation can be of interest to enhance clinical efficacy of transcranial stimulation[80,81]. Finally, in the literature there are only few studies that have investigated the clinical efficacy of tDCS in schizophrenia. Promising results have been reported but replication studies with larger samples are needed before any conclusion.

Obsessive-compulsive disorder

Obsessive-compulsive disorder (OCD) has a 2% lifetime prevalence in the general population[82,83]. Commonly, OCD symptoms begin during childhood and have a chronic course, causing severe impairments in both interpersonal and occupational functioning[84-86]. In addition, pharmacotherapy is only effective in 40%-60% of patients[87], and cognitive-behavior therapy (CBT),which has been reported as the most effective treatment for OCD[88], is not readily available to the majority of patients. Overall, 30% of OCD patients are refractory to any first or second line treatments[89]. Thus, the search for a clearer understanding of disease etiology and the need for new approaches to treatment-resistant patients are paramount.

It has been proposed that OCD results from mal-functioning of cortico-striato-thalamo-cortical circuitry including the medial prefrontal cortex (*i.e*., supplementary motor area-SMA and anterior cingulate cortex-ACC), the dorsolateral prefrontal cortex, orbitofrontal cortex (OFC), and basal ganglia[90]. This model informed neurosurgical approaches to OCD, and resulted in effective invasive treatments as evidenced by the FDA humanitarian use approval for high frequency deep brain stimulation (DBS) in treatment-resistant cases[91]. However, the need for noninvasive alternatives for patients who do not respond to standard treatments (*e.g.*, serotonin reuptake inhibitors or CBT) remains.

While rTMS has shown promise when applied to the SMA and to the OFC[92], tDCS has been less investigated for the treatment of OCD. Therefore, questions about which areas should be targeted and which parameters should be used still need to be addressed. In one case report, tDCS resulted ineffective when applied to the DLPFC[10], whereas a 30% reduction in the Yale-Brown Obsessive Compulsive Severity Scale was found in a case of treatment-resistant OCD after cathodal tDCS to the pre-SMA[93]. Furthermore, D'Urso *et al*[94] reported, in a randomized cross-over trial of anodal *vs* cathodal tDCS to the pre-SMA, that the cathodal application was significantly superior to anodal tDCS in reducing OCD symptoms. The results of this study are in line with findings of clinical efficacy of inhibitory rTMS to pre-SMA[95], demonstrated to be hyperactive in OCD patients during performance of cognitive tasks related to attentional aspects of action control[96,97].

The evidence deriving from the clinical efficacy of inhibitory rTMS and tDCS and from neurophysiological measures of altered motor cortex excitability in OCD[91], that normalized after 1-Hz rTMS to the pre-SMA[98], suggests that the pre-motor/motor system is abnormally hyperactive in OCD, and that there is a pathophysiological link between such hyperexcitability and OCD symptoms.

In this context, to optimize the effect of cathodal tDCS in OCD, simulated predictions of electric flow models would be an extremely useful strategy for the design of future tDCS trials. By applying this model, Senco *et al*[99] found that the application of the active electrode (cathode) over the pre-SMA, with the reference electrode (anode) positioned on an extracephalic location (*i.e.*, the subject's right deltoid), resulted in a distribution of the electrical field from the medial prefrontal cortex to the striatum, therefore reaching the cortical and subcortical brain areas which are crucially involved in the pathophysiology of OCD. Based on this model and on the promising results about the efficacy of cathodal tDCS to pre-SMA in treatment-resistant OCD, a randomized controlled trial testing the clinical and neurobiological effects of tDCS in OCD is underway.

TDCS in child psychiatry

The first onset of a variety of mental disorders diagnosed in adults occurs in childhood or adolescence, as for instance, impulse-control disorders, attention deficit hyperactivity disorder (ADHD), phobias, separation anxiety disorder and substance use disorder[100]. Earlier onset is associated with treatment delay, longer duration of illness and poorer clinical and functional outcomes, being an important cause of burden during this period of life[101,102]. In this sense, the use of novel treatments such as tDCS, should also be considered for children and adolescents, and might constitute a promising therapeutic and diagnostic tool, as the capacity for brain plasticity is greater during this period of life[103]. tDCS would be also an interesting tool to explore which brain areas are particularly important in each stage of development both in healthy and pathological conditions[7]. Nevertheless, the scope of literature in child and adolescent psychiatry is still very limited, with the majority of studies being case reports and open label studies.

An open study evaluating autistic patients with minimal verbal language have applied anodal tDCS over the Broca's area to improve language acquisition and the results showed that mean vocabulary scores were significantly higher after the intervention Schneider *et al*[104]. One double-blind, sham-controlled trial with 12 youths (age range from 10 to 17 years) with schizophrenia evaluated the tolerability of tDCS. The patients were assigned to anodal or cathodal stimulation and both groups were stimulated for 20 min per day during 10 d. Although no clinical improvement was observed, this protocol was well tolerated, without reports of serious side effects Mattai[105]. No study has assessed so far the effect of tDCS for the treatment of major depression in children and adolescents.

Attention deficit hyperactivity disorder is a behavioral diagnosis of early childhood where children often have changes in motor control development, and studies with adults suggested that anodal tDCS in the DLPFC may be associated with enhancement of cognitive performance[106]. Currently, there are an increasing number of studies investigating TMS as an evaluation and therapeutic tool in ADHD, but no studies regarding tDCS in children and adolescents with this diagnose.

During childhood and adolescence the developing brain is probably more sensitive to interventions. This might lead to better results comparing to adults, but also to an increased risk of side effects, related to possible negative or maladaptive plasticity[35]. For this reason, the application of tDCS in developmental age should be considered only after convincing evidence has been collected on adult populations, even when dealing with disorders usually first diagnosed in infancy, childhood, or adolescence. In the case of Autism, despite two reports of positive findings about the use of cathodal tDCS over the DLPFC for the treatment of some autism-related core behavioral symptoms D' Urso[107] no study has involved so far autistic patients in the developmental age. Nonetheless, neuroplasticity in important brain areas can hardly be controlled in RCT even when using widely accepted and traditional treatments as psychotropic medication, so that the only available way to gather adequate data on efficacy and side effects is testing directly the specific target population[2]. Indeed, a recently published review of literature regarding non invasive brain stimulation in childhood and adolescence highlighted the importance of systematic research in dose-finding, with sham-controlled, double-blinded studies that are capable to provide important information not available from open label studies[35].

Substance use disorders

The treatment of substance use disorders is usually difficult and challenging. The central reward pathway, critical in the mechanism of dependences, comprises the dopaminergic system including the mesolimbic cortical ventral tegmental area and projections to the nucleus accumbens and the prefrontal cortex[108,109]. Neuroimaging studies showed the important function of the prefrontal cortex in substance use disorders, being an important cortical structure in working memory and executive functions, two cognitive domains that are usually damaged in chemical dependencies[110]. In literature, only few studies have investigated the application of tDCS for the treatment of chemical dependencies. Nonetheless, these studies have shown a possible role of this technique for the treatment of these conditions, especially by stimulating the activity

of the prefrontal cortex. Thus, the efficacy of tDCS in treating substance use disorders deserves further investigation, as shown below.

Cocaine: Goriniet *et al*[111] used tDCS over the DLPFC in two samples of subjects (18 cocaine dependent users and 18 control subjects) to investigate the effects of increasing cortical excitability after right or left anodal stimulation. The subjects were randomized to receive left-anodal/right-cathodal stimulation, right-anodal/left-cathodal stimulation, or sham (placebo) stimulation; each session was delivered at least 48 h apart. The results showed that the activation of the DLPFC (left and right) results in the reduction of risky behaviors in both, patients and control subjects, in cocaine dependent users. The authors concluded that in the future tDCS could represent a valuable tool for intervention in users of cocaine.

Alcohol: A randomized sham-controlled study in which 13 subjects received three different types of bilateral stimulation of DLPFC with tDCS: (1) active anodal left and cathodal right tDCS; (2) active anodal right and cathodal left tDCS; and (3) sham tDCS, have shown a reduction of craving for alcohol in both active groups compared to the sham group[112].

Moreover, Klausset *et al*[113] studied 35 subjects randomized to receive active bilateral (left cathodal/right anodal over the DLPFC) repetitive (five consecutive days) tDCS (2 mA, 35 cm^2, two times daily stimulation for 13 min with a 20-min interval) or sham-tDCS. They observed that bilateral tDCS over DLPFC reduced relapse probability in severe alcoholic subjects and improved perception of quality of life.

Nicotine: Fregni *et al*[114] have investigated 24 patients, who received three different condition of a single tDCS session in a randomized order: sham stimulation, anode on the right DLPFC and anode the left DLPFC. The authors observed a reduction of craving in both active groups compared to the sham group.

Another study evaluated the effects of five consecutive sessions of tDCS on DLPFC. Twenty seven patients were randomized into two distinct groups: left anode and sham stimulation. The results showed a small but significant reduction in cigarette consumption and craving in active *vs* sham groups[115].

A more recent study showed that anodal stimulation over the left DLPFC improved smoking-related negative affect, but did not improve the fissure. The authors studied 24 smokers who received one real session and one sham session of tDCS after overnight abstinence from smoking in two different days. They applied anodal tDCS to the left dorsolateral prefrontal cortex and cathode to the right supra-orbital area for 20 min with a current intensity of 2.0 mA[116].

Fecteau *et al*[117] rated two five-day tDCS regimens (active or sham). Stimulation was delivered over the right DLPFC at a 2 mA during 30 min in twelve adults. The main finding was a significant reduction in the number of cigarettes smoked when participants received active as compared to sham stimulation.

Food: Fregni *et al*[118] conducted a study on healthy subjects who reported frequent food cravings. They designed a sham controlled crossover study, applying one session of tDCS stimulation (2 mA, 20 min) in three different conditions: anodal-left/cathodal-right DLPFC, cathodal-right/anodal-left DLPFC and placebo. They observed a reduction of cue-induced food craving when comparing active anodal left/cathodal right DLPFC over the other groups and a lower caloric ingestion when comparing active (both configurations) to sham group.

Goldman *et al*[119] applied 1 session of tDCS (2 mA, 20 min, anodal prefrontal dorsolateral cortex right) in healthy subjects that reporting food craving. The study showed a reduction of craving in both sham and active tDCS conditions. Moreover, the results indicated decreased ratings for specific food items when comparing active to sham tDCS.

Cannabis: Boggio *et al*[120] studied the effect of tDCS on cannabis dependence. Twenty-five patients were divided into three distinct groups: anode left/cathode right, anode right/cathode left and sham stimulation. The results showed a significantly decrease of the craving for marijuana in the anodal right stimulation group.

USE OF TDCS IN COGNITION

Results from several studies regarding the effects of tDCS stimulation suggest that it could induce clinical gains in major depressive disorder, schizophrenia and substance use disorders[121]. In many studies, researchers have noticed improvement in cognitive aspects of patients, such as working memory, attention, executive functions and processing speed[122]. Furthermore, reports have demonstrated its utility in the facilitation of several cognitive domains, such as implicit motor learning and visuo-motor learning[123,124], indicating its potential effectiveness on the modulation of behavior through the modulation of neurotransmitter-dependent plasticity on the network level.

The results of some studies in patients with major depression suggest improvement in performance Digits Test[125], increasing of correct responses in affective Go-no-go[51], improving of attention and working memory[49,63,126], cognitive control[127] and processing speed[126]. Some studies in patients with Alzheimer's disease showed improvement in recognition memory[127] and visual recognition memory Boggio *et al*[128,129] after stimulation with tDCS. One study reported an improvement in learning probabilistic membership functions in schizophrenic patients after tDCS[130]. Another study in 18 schizophrenic patients showed an improvement in working memory[131]. Finally, a study of alcoholic subjects showed that after five

weeks of stimulation, the subjects showed significant improvement in executive functions[132].

With the same logic that the effects of tDCS showed cognitive improvement in psychiatric and neurological patients, studies with healthy subjects have shown that tDCS can promote changes in cognitive function after only one session or even after a series of sessions[6]. Several studies have demonstrated the effects of tDCS on different cognitive functions in healthy subjects[133]. In order to study further the relationship between tDCS and cognition, some researchers have decided to study neural underpinning effects on cognition. Supported by the observation that anodal tDCS over the left DLPFC could improve naming performance in healthy participants[134] investigated the putative neurophysiological mechanisms underpinning language production. The authors found the reduction of semantic interference after anodal stimulation. Other studies have been conducted to explore the inhibitory effect of the technique[133].

This area of study may contribute in the future in the investigation of the application of tDCS as an important non-invasive tool for the rehabilitation of cognitive functions. However, the studies so far available suggest that the changes in cognitive performance observed after tDCS stimulation are short-lived; this warrants more studies to better explore the development of the application of tDCS in patients with neurocognitive disorders.

REGULATORY ISSUES

There are over 1200 tDCS publications in Pubmed, with more than 200 being clinical trials for multiple clinical disorders. The potential of tDCS for clinical practice has been demonstrated for psychiatric and cognitive disorders, as described above, for psychiatric conditions associated with neurologic disorders, such as depression in Parkinson diseases and stroke, but also for tinnitus, chronic pain and motor deficit due to different neurological diseases.

An interesting aspect of tDCS is that it has a low risk; it is simple to operate, being portable and having a relatively low cost. On the other hand these same characteristics increases the chance of misuse, such as enhancement application, recreational using and using without supervision (as discussed below in ethical issues), which increases the need for regulations concerning the use of tDCS.

A worldwide implementation of tDCS regulation is not straightforward, since each country follows its own medical, sanitary and legislatory rules. Commonly, the use of tDCS devices in research requires an approval by the local ethics committee, which, in several countries follows, at least partially, the World Medical Association-Declaration of Helsinki[135].

For clinical purposes, it is necessary the regulation of a new treatment according to the country's internal policies, which is based on ethical aspects, safety and clinical evidence of effectiveness. To our knowledge, there is no country that regulated the use of tDCS in clinical practice as an on-label treatment, although the evidence of the benefit of tDCS is increasing. For instance, a recent meta-analysis found that active tDCS was statistically superior to sham for treatment of acute depression[8]. The regulation in several countries tends to be very restrictive, since it is also used to determinate medical insurance coverage and public health politics. Moreover, in our opinion, tDCS device should be regulated as a medical device, since it fulfills the criteria for this, at least for the United States Foods and Drugs Administration[136].

Frequently, the regulation for clinical use also defines the professional category that could perform the therapy. We advocate that tDCS should have similar regulation of the psychotropic medications, since it has direct effect in the brain. In our opinion, the stimulation could be applied by trained technicians, but always with medical indication and supervision, although this is not necessarily a consensus in scientific community.

Although it is still necessary a better understanding of the parameters of stimulation and the long terms effect of tDCS for therapy, it is being already used in some countries as off-label and compassioned treatment. The use in this situation is normally justified by the lack of conventional treatment for neurologic and psychiatric diseases.

ETHICAL ISSUES

As all medical interventions in clinical practice and research, tDCS raises general and specific ethical issues that must be promptly addressed. Wider ethical issues regarding tDCS encompass the pillars of bioethics, namely, the principles of non-maleficence, beneficence, autonomy and justice[137]. Nonetheless, the definition and overall discussion of these paradigms surpass the scope of this section of the paper.

The specific ethical issues raised by the growing use of neuromodulation techniques, of which tDCS is a part, are plentiful. Topics particularly relevant are: the "cosmetic use" of tDCS as a cognitive-enhancement procedure (*i.e.*, for non-research or non-therapeutic objectives), the hypothetical long-term effects of tDCS on other mental faculties of its recipients, and the inappropriate assemblage and use of tDCS devices by nonmedical population, in nonclinical settings[7,138,139].

There are several medical interventions (both pharmacological and non-pharmacological) aimed at improving cognitive faculties in some neuropsychiatric disorders. For instance, methylphenidate is medically approved to treat ADHD, and thereby improve the patient's ability to concentrate and appropriately conclude tasks. On the other hand, this drug is knowingly misused by healthy populations, who end up taking it to improve their performance in situations like academic presentations and exams. The same phenomenon

could occur with tDCS. Consequentially, an intervention initially devised to treat pathological conditions, such as major depressive disorder, and lead to recovery of secondary cognitive deficits, might mistakenly be used for cosmetic cognitive enhancement[138].

The major concern about the indiscriminate use of tDCS, especially for cosmetic purposes, is that since it is a relatively novel method, and in many ways still in phases of research, its long-term side effects are not completely known. Despite its notorious short-term safety with minimal and benign side effects, there is preliminary evidence pointing to possible and unforeseen interference of tDCS with the individual's social cognition[139], moral judgment[140] and even the capacity to tell the truth or deceive others[141]. While such effects might be of minimal clinical relevance when tDCS is applied correctly in clinical settings, with adequate monitoring of individual responses, the same cannot be said about its cosmetic use.

Finally, it is important to recognize that while the equipment necessary to perform other neuromodulatory techniques is expensive and not portable (rTMS, for instance), naturally limiting their use in nonclinical settings, the device used in tDCS is lightweight, portable and can be assembled inexpensively[138]. Moreover, it can be used at home, and in fact, there are websites and open discussion groups aimed at instructing nonmedical population on how to independently apply tDCS on oneself.

Therefore, as the practice of tDCS becomes widespread, physicians and researchers need to be very attentive to its correct clinical use, its long-term effects on cognition, moral judgment and personality, and cooperate with governmental regulation regarding the manufacture and commercialization of its devices and apparel. Needless to mention, all to safeguard the appropriate autonomy of our patients, while helping them make the best decisions with regard to their mental and physical health.

CONCLUSION

We hereby presented an overview of tDCS use in psychiatry, from its history, through the mechanism of action, results in different fields of psychiatry, ethical considerations and methodological aspects were presented. The main point of emphasis, perhaps, for this conclusion is tDCS clinical research - particularly randomized controlled-trials, began to be researched in psychiatry only recently. Even being a technique that has a recent scientific and clinical interest, it has already demonstrated that it might be a promising tool in the therapeutic arsenal of psychiatric disorders.

The interest, both academic as of the lay public and the media around the tDCS has increased considerably in recent years[142]. This interest will probably continue to increase, given the promising results that the technique has presented in psychiatry and also in other field, such as neurology[143]. Along with promising results, comes the excitement and interest of the media. The ethical aspects surrounding the tDCS is being intensively discussed. This is necessary to maintain scientific rigor in terms of the information that reaches the lay public[142].

With the promising results found in different psychiatric disorders, further studies, with robust methodologies, should strive to replicate, expand and optimize the findings, perhaps testing larger, different samples and also varying tDCS parameters such as electrode size, dosage, reference electrode, length of sessions, number of days of application are still warranted in order to provide a definite picture regarding tDCS clinical efficacy in psychiatry.

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REVIEW

Postpartum depression: A systematic review of the genetics involved

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Abstract

Postpartum depression is one of the most prevalent psychopathologies. Its prevalence is estimated to be between 10% and 15%. Despite its multifactorial etiology, it is known that genetics play an important role in the genesis of this disorder. This paper reviews epidemiological evidence supporting the role of genetics in postpartum depression (PPD). The main objectives of this review are to determine which genes and polymorphisms are associated with PPD and discuss how this association may occur. In addition, this paper explores whether these genes are somehow related to or even the same as those linked to Major Depression (MD). To identify gaps in the current knowledge that require investigation, a systematic review was conducted in the electronic databases PubMed, LILACS and SciELO using the index terms "postpartum depression" and "genetics". Literature searches for articles in peer-reviewed journals were made until April 2014. PPD was indexed 56 times with genetics. The inclusion criteria were articles in Portuguese, Spanish or English that were available by institutional means or sent by authors upon request; this search resulted in 20 papers. Genes and polymorphisms traditionally related to MD, which are those involved in the serotonin, catecholamine, brain-derived neurotrophic factor and tryptophan metabolism, have been the most studied, and some have been related to PPD. The results are conflicting and some depend on epigenetics, which makes the data incipient. Further studies are required to determine the genes that are involved in PPD and establish the nature of the relationship between these genes and PPD.

Key words: Genetics; Single nucleotide polymorphisms; Molecular; Postpartum depression; Genes

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Core tip: *5HTT* and *5HTTLPR* were the most studied gene and polymorphism, respectively. 5HTTLPR is associated with postpartum depression (PPD) in the majority of papers, but epigenetics must be considered. TPH1 and TPH2 polymorphisms are related to peripartum depression. COMT and MAOA polymorphisms were also risk factors for PPD. Once again, only when epigenetic was analyzed, an association with BDNF polymorphism was possible. MTHFR, CYP2D6 and PER2 polymorphisms were not related to this mood disorder. Polymorphisms of oxytocin, steroids and estrogen genes were positively correlated with PPD.

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INTRODUCTION

Historically, pregnancy and puerperium have been considered periods that protect women from mental disorders. It is now known that the opposite is true: those periods confer a higher risk of appearance and recurrence of mental disorders and should therefore be a public health concern. Postpartum depression (PPD) is one of these disorders. Epidemiological papers demonstrated that the prevalence of postpartum depression is between 10% and 15%[1-3].

The adverse impacts of PPD are not limited to mothers; PPD also affects other family members and influences family dynamics. Recent studies have shown that PPD can also lead to significant language, cognitive and emotional processing problems in children[4-6]. Psychopathologies in children may not be restricted to the first years of life; it is possible to find manifestations, such as conduct disorder, that persist even until adolescence[7]. The partners of women with PPD also tend to have depression more frequently than expected[8,9].

Psychological and social changes mark the transition to motherhood. Those changes, together with clinical history and obstetrical aspects, may be related to PPD. Self-esteem, childcare stress, life stress, social support, marital relationship, infant temperament, marital status, socioeconomic status, unplanned/unwanted pregnancy[10], previous psychiatric disorder[1,10], method of childbirth, and previous abortion[11] are the main findings associated with PPD.

In addition, biological changes are related to PPD. According to some investigations, these changes may be partly genetically determined. A study conducted in England evaluated 44 pairs of sisters who had unipolar depression and found that those pairs in which one sister fulfilled the PPD criteria according to DSM-Ⅳ, 42% of the other sisters developed PPD after giving birth. For those who had no family history of depression, the rates dropped to 15% (P = 0.01). In this study, the evidence of a genetic influence is even greater when the PPD period was restricted for 6 to 8 wk postpartum[12]. Another study, conducted in Australia, involved the interview of 838 pairs of adult twins about their postpartum experiences. The authors reported that genetic factors explained 25% of the variance in the occurrence of PPD[13]. Over the last decade, many studies have been devoted to verifying the impact of this type of genetic variation in PPD, and it is thus important to know the concept of Single Nucleotide Polymorphisms (SNPs). SNP is a genetic variation that affects only one base pair in the DNA sequence. These variations in DNA sequence can affect the individual response to diseases, bacteria, viruses, chemicals, pharmaceuticals. To be considered an SNP, the variation should occur in at least 1% of a given population.

The present report aims to assess molecular studies associated with PPD and highlight the most studied genes and polymorphisms.

RESEARCH

The present paper is a systematic, integrative review that includes several studies with different methodologies to answer questions about the relationship between genetic factors and the development of postpartum depression. For guidance, the following questions were raised: Are there genes or polymorphisms that are more related than others to postpartum depression? What is their relevance? Are Major Depression (MD) and Postpartum Depression the same or different disorders? Is PPD only a temporal variant of MD?

This study consisted of a search of all articles describing a clear relationship between genetics and postpartum depression that were indexed in PubMed, LILACS and SciELO published before April 2014.

To accurately answer the questions that guided this review, the abstracts were read and classified during a selection process. If, after reading the abstract, there was reasonable doubt about the inclusion or exclusion of the paper, the whole article was read. The same procedure was adopted when abstracts were not available. Thereafter, a reverse search was carried out.

The following inclusion and exclusion criteria were used.

Included: papers in Portuguese, Spanish or English in the researched databases, with index terms "postpartum depression" and "genetics", which assessed the genes and polymorphisms related to PPD. For this purpose, the following algorithms were used: ("Depression, Postpartum"[Mesh]) AND ("Genetics"[Mesh] OR "genetics"[Subheading]).

Excluded: review articles and animal models; articles that were not available by CAPES (Brazilian governmental agency that sponsors studies) and not provided by authors upon request; those that researched another postpartum psychopathology, finding or result; and those that did not address genetics involved in PPD.

RESULTS

The LILACS and SciELO searches did not result in any article fulfilling the criteria. The PubMed search resulted in 56 papers. After reading the abstracts, 36 were excluded: 6 reviews[14-19], 2 papers that were not available by CAPES and not sent by the authors upon request[20,21], 5 animal models[22-26], 12 investigating another postpartum psychopathology (psychoses and bipolar)[27-38], 3 evaluating the children[6,39,40], 1 on breastfeeding[41] and 7 that did not address the genetic factors involved in PPD[12,13,42-46]. A reverse search resulted in no additional items. Finally, a sample was formed[47-66].

The 20 selected studies were conducted in 10 different countries. Sweden[48,50,53] and the United States of America[49,57,64] had three publications each (15%). Germany[56,61], China (Taiwan)[55,60], Spain[51,58], Canada[63,66], the United Kingdom[54,65] and Brazil[47,62] had two papers each (10%). Israel[59] and Netherlands[52] had one paper (5%) each (Table 1).

Of the selected sample, the *5HTT* gene was the most studied[48-50,52,56-58,66]. Genes associated with tryptophan metabolism[55,60,61,66] and Catechol-O-methyl transferase (COMT)[48,52,62,66] were the next most researched. Monoamine Oxidase (*MAO*) gene was studied in three of the articles included in this review[48,52,66], and the Brain-Derived Neurotrophic Factor (*BDNF*) gene was studied in two articles[47,50]. Two articles analyzed genes that are not commonly evaluated in depression studies: the Methylenetetrahydrofolate Reductase (*MTHFR*) gene[54] and the *CYP2D6* gene[53]. One article was about circadian gene *Per* 2[50], and one was about the oxytocin gene (*OXT*) and oxytocin receptor gene (*OXTR*)[63]. Costas *et al*[51] assessed 44 genes involved in pathways that are hypothetically related to the etiology of postpartum mood disorders, that is, those included in the HPA axis, in the effects of stress in the prefrontal cortex, and in the regulation of sex hormones. Looking for an association between PPD and the HPA axis, Engineer *et al*[65] tested the glucocorticoid (*GR*) and type 1 corticotropin-releasing hormone (*CRHR1*) receptor genes. Based on the results of Costas' paper, Pinssoneault *et al*[66] researched the *ESR1* gene both as a principal outcome and under the additive power of other genes: *COMT*, *TPH2*, *MAOA*, *5HTT*, dopamine receptor D2 (*DRD2*), serotonin receptor 2A (*HTR2A*) and dopamine transporter (*DAT*). An Israeli study evaluated peripheral blood mononuclear cell (*PBMC*) gene expression[59]. Finally, an American study analyzed 417 microsatellite markers in linkage studies and chromosomes 1 and 9 by Genome-Wide Association Studies (GWAS)[64].

The most studied polymorphism was the 5-HTTLPR, which was addressed in eight articles[48-50,52,56-58,66]; some of these articles also analyzed other polymorphisms in the 5HTT, such as STin2 VNTR[57,58] and rs140700[51]. The remaining studied polymorphisms were those of *TPH* 1 and 2[55,60,61,66], *COMT*[48,52,62,66], *MAO*[48,52,66], *BDNF*[47,50], *CYP2D6*[53], *MTHFR*[54], *Per* 2[50], *OXT*/*OXTR* genes[63] and *GR*/*CRHR1* genes[65]. Pinssoneault *et al*[66] adopted a different strategy: in addition to looking for polymorphisms of the estrogen receptor alpha gene (*ESR1*), they looked for associations with the polymorphisms already cited in this report (MAOA, COMT, TPH2, 5HTTLPR SNPs) besides those of the genes *HTR2A*, *DAT* and *DRD2*[66]. Segman *et al*[59] used a different approach, analyzing not polymorphisms but 3142 active transcripts, whereas Mahon *et al*[64] studied 16.916 SNPs through GWAS (Table 1).

DISCUSSION

The data regarding *5HTT* gene polymorphisms were variable. Doornbos *et al*[52] performed the only study that found an independent relationship between PPD and the 5HTTLPR polymorphism whereby subjects with the 5HTTLPR long allele variable developed PPD. Binder *et al*[49] and Sanjuan *et al*[58] found a significant association between 5HTTLPR and PPD only at 8 wk postpartum, but the results became nonsignificant in a posteriori analysis, suggesting that the findings were dependent on the evaluation time point. The remaining 5HTTLPR studies also depended on covariates to achieve statistically significant associations with PPD: unfavorable environments[57]; previous psychiatric history, maternity stressors and COMT-Val158Met allele[48]; autumn or winter delivery[50]; stressful life events[56]; and a gene-gene interaction with ESR1 TA repeat[66].

The *TPH* gene study showed a significant difference in genotype frequency for the T27224C polymorphism between standard groups and those with comorbid depression and anxiety, with risk analysis showing that the C allele conferred a strong protective effect for depression and anxiety. This finding suggests that the *TPH1* gene has an important role in the pathogenesis of postpartum mental disorders[60]. Similarly, one of the *TPH2* gene studies attested that the C2755A polymorphism could be considered a risk factor for depression. The C2755A polymorphism occurred only in women with peripartum major depression and anxiety disorders (P = 0.043) and exhibited a dominant gene action (P = 0.038) with an estimated disease risk of 1.73. Hence, despite its small sample size, this study suggests that TPH2 represent a population-specific risk factor for peripartum major depression[55]. A recent study supports that conclusion; it found that a haplotype block in the promoter region of TPH2 showed significant associations with

Table 1 Genes and polymorphisms associated with postpartum depression

Article	Ref.	Country	Instrument	Genes	Polymorphisms
CYP2D6 genotypes and depressive symptoms during late pregnancy and postpartum	Josefsson *et al*[53]	Sweden	EPDS	*CYP2D6*	CYP2D6*1 (wild type), CYP2D6*3, CYP2D6*4
Association of tryptophan hydroxylase gene polymorphism with depression, anxiety and comorbid depression and anxiety in a population-based sample of postpartum Taiwanese women	Sun *et al*[60]	China	SADS	*TPH1*	T3840A, A12517C, A20004C, G347T, T27224C
Mood changes after delivery: role of the serotonin transporter gene	Sanjuan *et al*[58]	Spain	EPDS/DIGS	*5HTT*	5HTTLPR, STin2 VNTR
The development of peripartum depressive symptoms is associated with gene polymorphisms of MAOA, 5-HTT and COMT	Doornbos *et al*[52]	Netherland	EPDS	*MAOA*, *5HTT*, *COMT*	MAOA , 5HTTLPR, COMT Val158Met
Population-specific functional variant of the TPH2 gene 2755C>A polymorphism contributes risk association to major depression and anxiety in Chinese peripartum women	Lin *et al*[55]	China	SADS	*TPH2*	T-703G, T-473A, A90G, C2755A, C10662T, G93329A
Genome-wide linkage and follow-up association study of postpartum mood symptoms	Mahon *et al*[64]	United States	DIGS		417 microsatellite markers in linkage studies / 16.916 SNPs in the 1 and 9 chromosomes for GWAS.
Blood mononuclear cell gene expression signature of postpartum depression	Segman *et al*[59]	Israel	EPDS	*PBMC* gene expression	3142 active transcripts set
A serotonin transporter gene polymorphism predicts peripartum depressive symptoms in an at-risk psychiatric cohort	Binder *et al*[49]	United States	SCID/ HRSD-17	*5HTT*	5HTTLPR
Association study of 44 candidate genes with depressive and anxiety symptoms in post-partum women	Costas *et al*[51]	Spain	EPDS/DIGS	44 genes involved in pathways hipothetically related to the etiology of postpartum mood disorders: HPA axis, effects of stress in the prefrontal cortex, and regulation of sex hormones	388 SNPs
An association study between the Val66Met polymorphism of the BDNF gene and postpartum depression	Figueira *et al*[47]	Brazil	EPDS	*BDNF*	BDNF Val66Met
Postpartum depression symptoms: a case-control study on monoaminergic functional polymorphisms and environmental stressors	Comasco *et al*[50]	Sweden	EPDS	*COMT*, *MAOA*, *5HTT*	COMT Val158Met, MAOA uVTNR, 5HTTLPR.
Role of mother's genes and environment in postpartum depression	Mitchell *et al*[57]	United States	CIDI-SF	*5HTT*	5HTTLPR , STin2 VNTR
Postpartum depressive symptoms and the BDNF Val66Met functional polymorphism: effect of season of delivery	Comasco *et al*[50]	Sweden	EPDS	*BDNF*, *5HTT*, *PER2*	BDNF Val66Met, PER2 SNP 10870 (G and A), 5HTTPLR (L and S)
Folic acid supplementation during pregnancy may protect against depression 21 months after pregnancy, an effect modified by MTHFR C677T genotype	Lewis *et al*[54]	England	EPDS	*MTHFR*	C677T
The 5-HTTLPR polymorphism modulates the influence on environmental stressors on peripartum depression symptoms	Mehta *et al*[56]	Germany	EPDS	*5HTT*	5HTTLPR

Genetic variants in the tryptophan hydroxylase 2 gene (*TPH2*) and depression during and after pregnancy	Fasching *et al*[61]	Germany	EPDS	*TPH2*	rs11178993, rs6582071, rs11178997, rs7955501, rs17110536, rs4760814, rs7300641, rs4760820, rs10879354, rs1487275, rs10879358, rs11615016, rs17110747, rs1872824
Postpartum depression symptoms associated with Val158Met COMT polymorphism	Alvim-Soares *et al*[62]	Brazil	EPDS	*COMT*	COMT Val158Met
Interaction between oxytocin genotypes and early experience predicts quality of mothering and postpartum mood	Mileva-Seitz *et al*[63]	Canada	CES-D	*OXT, OXTR*	OXT: rs2740210, rs4813627/ OXTR: rs237885
Association of glucocorticoid and type 1 corticotropin-releasing hormone receptors gene variants and risk for depression during pregnancy and post-partum	Engineer *et al*[65]	United Kingdom	EPDS	*GR, CRHR1*	GR: BclI, ER22/23EK/CRHR1: s1876828, rs242939, rs242941
Association study of the estrogen receptor gene *ESR1* with postpartum depression - a pilot study	Pinsonneault *et al*[66]	Canada	MINI, SCID, *EPDS* and/or *MADRS*	*ESR1, COMT, TPH2, DRD2, HTR2A, DAT, MAOA, 5HTT*	ESR1: TA repeat, rs2077647, rs1801132, rs3798577, rs988328, rs1884051, rs3020327, rs9340958, rs3020434/ HTR2A: rs6314, rs6311/DAT: rs27072, rs6347, In8VNTR/ 5HTTLPR/MAOA: rs1137070, pVNTR/TPH2: rs7305115 / DRD2: rs2283265 / COMT: rs4680

EPDS: Edinburgh Postnatal Depression Scale; SADS: Schedule for Affective Disorders and Schizophrenia; DIGS: Diagnostic Interview for Genetics Studies; SCID: Structured Clinical Interview for DSM-IV; HRSD-17: 17-item Hamilton Rating Scale for Depression; CIDI-SF: Composite International Diagnostic Interview-short form; CES-D: Center for Epidemiological Studies Depression Scale; MADRS: Montgomery-Asberg Depression Scale; TPH: Tryptophan hydroxylase; 5HTT: Serotonin transporter; MAOA: Monoamine oxidase A; COMT: Catechol-O-methyltransferase; PBMC: Peripheral blood mononuclear cell; BDNF: Brain-derived neurotrophic factor; PER2: Period circadian clock 2; MTHFR: Methylenetetrahydrofolate reductase; OXT: Oxytocin; OXTR: Oxytocin receptor; GR: Glucocorticoid receptor; CRHR1: Type 1 corticotropin-releasing hormone receptor; ESR1: Estrogen receptor alpha; DRD2: Dopamine receptor D2; HTR2A: Serotonin receptor 2A; DAT: Dopamine transporter.

depression values during pregnancy and 6-8 mo after pregnancy[61]. This last paper also showed that the SNP rs10879354 had a significant association with depression throughout the postpartum period. A gene-gene interaction with *ESR1* gene was not found[66].

Four papers focused on the COMT genes[48,52,62,66], with three of them also focusing on the *MAOA* gene[48,52,66]. COMT-Val158Met allele polymorphism was one of the main risk factors for PPD[48,52,62], despite not being an independent risk factor[48,52,66]. Previous psychiatric contact, maternity stressors and the time of the evaluation (6 wk or 6 mo postpartum) influenced the relationship[48]. Similarly, the interaction with MAOA - L polymorphism was associated with more pronounced depressive symptoms than when the COMT-Val158 Met allele was considered alone[52]. MAOA rs1137070 and COMT rs4680 polymorphisms were found to have an additive effect plus ESR1 in producing PPD[66].

Figueira *et al*[47] and Comasco *et al*[50] did not find any linear correlation between PPD and the BDNF ValMet polymorphism. The correlation showed a trend toward significance among Met allele carriers[47,50]. There was a cumulative and significant effect of the presence of Met allele and autumn/winter delivery[50].

The C677T polymorphism was also studied in a study that focused on the association between MTHFR and PPD. Its results indicated that low folate levels do not appear to be a significant risk factor for peripartum depression but may be a factor for non-gestational-related depression, especially in women with the MTHFR C677T TT genotype[54]. The study on CYP2D6 showed that in a sample that included 45 women reporting symptoms of depression only during pregnancy, 56 women reporting symptoms of depression only after pregnancy and 44 women reporting symptoms of depression both during and after pregnancy, there were no differences in CYP2D6 genotyping and depressive symptoms[53].

Circadian genes did not appear to have a "family" effect. Despite the correlation between postpartum depressive onset in bipolar disorder and Per3 4/4 homozygotes[37], the circadian gene *Per* 2 was not related to PPD[50].

As in Major Depression[67], the *OXTR* gene appears to be related to perinatal depression. Its SNP rs237885 was associated with pre-natal, but not post-natal, depression scores[63]. There was also a correlation between OXT SNPs rs2740210 and rs4813627 and depression score 6 mo after delivery. However, this finding seems to be mediated by mother's early life quality of care because the association was not retained in the regression model. That is, these appear to be separate effects

rather than causally linked outcomes[63].

Costas *et al*[51] studied 44 genes that are hypothetically linked to depression and, after correcting for multiple tests, did not find a significant relation between any of the SNPs tested and PPD. Nevertheless, a post hoc analysis showed that a combination of three SNPs of the protein kinase C beta gene (*PRKCB*): rs198183, rs381901 and rs2051684, achieved statistical significance (global P = 0.0001596)[51], turning it into a potential target.

The GR polymorphism BclI, but not the ER22/23EK, showed a positive association with high EPDS score and, therefore, PPD. This correlation was also positive for the minor allele rs242939 SNP of the *CRHR1* gene, with the particularity that a relation with prenatal EPDS score could also be found in this case[65]. This result supports Brummelte and Galea's statement that there are changes in all aspects of the HPA system (ACTH, CRH and cortisol) during pregnancy and the postpartum period. Women who are susceptible to HPA axis dysregulation may be particularly vulnerable for developing stress-related disorders at this time[68].

Two variants in the *ESR1* gene, the TA repeat and rs2077647, were statistically associated with EPDS scores and PPD[66], suggesting that estrogen-linked molecular mechanisms could also be involved in PPD genesis. Conversely, gene-gene interactions detected with encoding serotonergic signaling proteins (5HTT and HTR2A) reinforce serotonin's contribution to PPD.

Segman *et al*[59], analyzing *PBMC* gene expression and its 3142 active transcripts, found a signature of 73 active transcripts showing 1.5-fold or higher significant association with PPD. Of those, a subsample of 57 transcripts remained significant in the secondary analysis. Despite the small sample size of the study, both the 73 and 57 differential transcript sets (but not the 3142) correctly distinguished PPD patients from controls. This capability could be used as a prognostic tool, allowing for the initial screening of mothers who are at higher risk for PPD development.

Finally, Mahon *et al*[64] used linkage and GWAS techniques and found that the chromosomes 1q21.3-q32.1 and 9p24.3p22.3 were associated with postpartum depressive mood. The authors suggest that Hemicentin 1 (*HMCN1*) and Methyltransferase like 13 (*METTL13*) genes on chromosome 1 contain polymorphisms that confer vulnerability for PPD, highlighting the notion that specific studies of those genes should be attempted[64]. These results must be watched with caution because bipolar patients with postpartum depressive onset were mingled in the sample. However, a study published last month also confirmed that an HMCN1 polymorphism (rs2891230) is associated with PPD diagnosis in a population without bipolar diagnosis[69].

Despite the substantial number of genes and polymorphisms reviewed here, there are still others that need testing. For instance, Maguire *et al*[24] noticed a relationship between GABAA receptor plasticity during pregnancy and PPD and proposed an animal model using $GABA_AR$ δ subunit deficient mice. Therefore, GABAergic genes may also be potential targets[24]. Another important genetic mechanism involved in Major Depression and not tested in PPD studies is the course of inflammation genes. Because functional allelic variants of the genes for IL-1β and TNF-α increase the risk for depression and are associated with reduced responsiveness to antidepressant therapy[70-72], their influence under PPD would be interesting to measure.

Overall, all of the articles selected had large sample sizes, thus rendering reliable results. Some of the differences found for the same polymorphism may be attributed to different methods used for PPD diagnosis, as observed in table 1. Another important point to note is that it seems, as in other psychiatric disorders, that genetic influence appears not to be sufficient by itself to cause the disorder. The development of psychiatric disorders is often dependent on epigenetics, and an environmental trigger is often required for these diseases to develop[48,50,57].

Riecher-Rössler *et al*[73] stated that there is no doubt that sex and gender, with their biological and psychosocial correlates, strongly affect mental health, given the marked difference regarding the prevalence, symptoms, risk factors and outcomes of psychiatric disorders between the sexes. Nevertheless, using PPD as an example, the author shows that such influence is necessary to ensure better clinical care and not to justify the existence of a distinct diagnostic entity. It was possible to demonstrate that the factors used to define "true" or "valid" psychiatric disorders: descriptive validity (the same symptoms), construct validity (the same risk factors) and predictive validity (the same course) are not satisfied in PPD[73]. MD and PPD apparently share the same genetic background because PPD seems to be linked to MAO, COMT, 5HTT and other pathways usually related to MD. In our opinion, this strengthens the possibility that they are the same disorder with a temporal variant[74,75]. However, there are not sufficient published data to determine whether there is a specific etiological factor that is capable of differentiating those two disorders. Further studies are needed to nullify this hypothesis, and for that, other candidate genes must also be researched.

CONCLUSION

This review summarizes the representative findings in the literature regarding the genetics involved in Postpartum Depression.

The main conclusion of this review is that similar genes tend to be studied in Postpartum Depression and that these genes have a similar pattern to those already associated with Major Depression in the literature.

The relationship between molecular genetics and PPD is an extremely current issue. The oldest article selected was from 2004, and the newest was from 2013. However, there is still little research in this area

compared with other psychiatric disorders, and it deserves further study due to its importance in terms of public health.

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MINIREVIEWS

Review of the genetic basis of emotion dysregulation in children and adolescents

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Abstract

Previous evidence suggests that emotion dysregulation may have different biological correlates between adults and children/adolescents. Although the role of genetic factors has been extensively studied in adult-onset emotion dysregulation, the genetic basis for pediatric-onset emotion dysregulation remains elusive. The current review article presents a summary of previous studies that have suggested a few genetic variants associated with pediatric emotion dysregulation. Among these candidate loci, many prior studies have been focused on serotonin transporter promoter gene polymorphism *5-HTTLPR*. Certain alleles of the *5-HTTLPR* gene polymorphism have been found to be associated with traits associated with emotion dysregulation, such as aggression, affect reactivity, and insecure attachment. Additionally, genetic variants involving dopamine and neurophysiological biomarkers like the *COMT* Val158Met (rs460) and dopamine receptor D2/ ankyrin repeat and kinase domain containing one polymorphisms may play a role in emotion dysregulation. Inconsistent findings have been noted, possibly due to the heterogeneity in study designs and characteristics of different populations. Further research on the role of genetic predetermination of emotion dysregulation in children and adolescents is warranted.

Key words: Gene; Emotion regulation; Adolescents; Children; *5-HTTLPR* polymorphism

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Core tip: Genetic correlates involved in emotion dysregulation in children and adolescents remain rather understudied compared to adult populations, despite the strong impact emotion dysregulation can have on an individual and societal functioning. This paper covers the key genetic variants involved in pediatric emotion dysregulation, with a special emphasis on the serotonin transporter promoter gene polymorphism *5-HTTLPR* typically associated with aggression, affect reactivity, and emotion dysregulation. This review places emphasis on

the necessity for further research in this field of study in order to better understand biological mechanisms underlying emotion dysregulation in children and adolescents, and also highlight current avenues of study worthy of further investigation.

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INTRODUCTION

Emotion dysregulation results from a failure to control, evaluate, and modify an emotional response to a stimulus, in particular the timing and severity of emotion, which often impacts externalizing behaviors[1]. In children and adolescents, emotion dysregulation can be considered the outcome of the tendency to respond emotionally to a stimulus combined with the ability to most successfully modulate the response[2]. These processes include conscious and subconscious mechanisms based in underlying genetic and neuro-physiological entities. With the advances of high-throughput and high-resolution genomic technologies, research on the genetic basis of mood dysregulation has been increasing and empowering researchers to better understand how and why this dysregulation occurs in children and adolescents. Prior evidence has suggested that pediatric-onset form and adult-onset form of bipolar disorder, which is characterized by emotion dysregulation, may have distinct genetic predispositions and clinical outcomes[3,4]. The purpose of this review is to summarize current genetics research findings within pediatric populations on emotion dysregulation and point out the need of more research to improved our understanding of genetic factors for pediatric emotional dysregulation. Unraveling age-dependent genetic mechanisms underlying emotion dysregulation will provide an initial step towards personalized medicines for mood disorders in children and adolescents. Although the body of research on genetic basis of pediatric-onset emotion dysregulation is limited compared to genetics research on emotion dysregulation in adults, several candidate genes have been consistently shown to be linked to emotion dysregulation in children and adolescents.

RESEARCH STUDY

A literature search with the key words related to genetic of emotion dysregulation in pediatric populations was conducted to gather information for this review article. Our query algorithm implemented in PubMed was as follows: required keywords were present in either "Abstract" or "Title" included (1) gene; (2) children or adolescents; and (3) emotion or mood followed by regulation, reactivity, or arousal. Additionally, only human-based studies with English as the language were extracted. Certain parts of research from this review were selected and modified from a lecture written for Continuing Medical Education to Go for Physicians. A total of 19 studies were retrieved. Selected studies related to the genetics of pediatric emotion dysregulation are summarized in Table 1.

SEROTONIN TRANSPORTER GENE 5-HTTLPR POLYMORPHISM

The serotonin transporter gene (*5-HTT*) and a polymorphic serotonin-transporter-linked polymorphic region (*5-HTTLPR*) determine the quantity and duration of serotonin synaptic signaling during neurotransmission[5]. There are three important variants of *5-HTTLPR* alleles: the short (S) allele, the long-rs25531(G) (La) allele, and the long-rs25531(A) (La) allele. The short (S) allele and the long-rs25531(G) (Lg) allele carriers[6] compared to the long-rs25531(A) (La) allele variant carriers, have lower mRNA transcriptions of the serotonin transporter. Individuals without an La allele are found to produce approximately 50% less mRNA than individuals carrying homozygous La alleles[7]. This polymorphism has been shown to correlate with the severity of affect reactivity and mood dysregulation[8]. A meta-analysis of a serotonin transporter genotype and the activity of amygdala, a brain region modulating emotion regulation, reports that the *5-HTTLPR* polymorphism accounts for 10% of the variance of amygdala activation[9]. Furthermore, the S allele has been shown to correlate with heightened amygdala activation in response to a broad range of emotional stimuli[9,10]. In a study of 82 children and adolescents, individuals carrying either S or Lg allele were found to have more than two times the risk of aggressive behavior than individuals carrying at least one La allele[5]. Borderline personality disorder, which is characterized by emotion instability, is also found to be associated with the short allele of the *5-HTTLPR* polymorphism[11]. Another study on 91 adolescents reported that the effect of the short allele of *5-HTTLPR* on aggressive behaviors might be modified by attachment[12]. These findings suggest that the *5-HTTLPR* polymorphism plays a role in emotion regulation, while environmental factors may also moderate its effect on mood symptoms and associated behaviors. More research is needed to validate these findings to have a better understanding of the role of this polymorphism in emotion regulation.

The *5-HTTLPR* polymorphism may also affect the cortical-limbic circuit critical for emotion regulation[13]. Diffusion MRI examining the uncinate fasciculus, a white matter pathway that connects medial and orbitofrontal prefrontal cortexes to amygdala, in 37 female adolescents and adults and found the number of short alleles at *5-HTTLPR* inversely correlate with

Table 1 Summary of emotion dysregulation genetic correlates in children and adolescents

Genetic neural correlates	
5-*HTTLPR* low-expressing allele carriers	
Pacheco *et al*[13]	Reduced white matter connectivity/density in uncinate fasciculus
Spangler *et al*[16]	Increased risk for development of disorganized attachment pattern
Gotlib *et al*[21]	Prolonged cortisol activity after a stressor
COMT Val156Met(rs460) Met Allele Carriers	
Boettinger *et al*[27]	Greater emotion dysregulation associated with dopaminergic systems
Waugh *et al*[24]	
Egan *et al*[25]	
Tunbridge *et al*[26]	
DRD2/ANKK1 Polymorphism	
Althaus *et al*[28]	5-HTTLPR S allele may predispose to (performance) anxiety, while DRD2 Taq1 A allele may predispose to the reward deficiency syndrome.

the fractional anisotropy (FA) values at white matter microarchitecture, especially in the left frontal region of the uncinate fasciculus. Uncinate fasciculus is a region believed to be the impetus behind the heightened amygdala reactivity and poorer functional coupling of amygdala and prefrontal cortex associated with emotion regulation abilities[13]. In addition, age is positively correlated with FA values in the bilateral frontal regions of the uncinate fasciculus-which is consistent with data showing the increase in prefrontal activity and thereby emotion regulation due to myelination and development of prefrontal cortex during adolescence and adulthood[13,14]. To date, there is no published evidence for the same phenomenon in males. Children carrying homozygous S alleles in the *5-HTTLPR* polymorphism are also found to have greater activity of amygdala during visual processing of emotionally negative stimuli that mimics a transient depressed state than their peers carrying homozygous L alleles[15].

Social and environmental adversity may also notably impact neuronal gene expressions (*i.e.,* epigenetic phenomena). Carriers of the S allele of *5-HTTLPR* polymorphism have an increased risk for developing disorganized attachment patterns in comparison to homozygous L genotypes, while maternal responsiveness mediated the effect and acted as a type of safeguard against disordered attachment genetic predisposition[16]. The study reveals that adolescents carrying the S allele show a greater emotional reactivity in response to restrictions of autonomy (defined as one's own goals as a method of self-regulation), compared with others carrying no S alleles[12]. Another study found that childhood emotional abuse significantly moderated the relationship between genotype and the likelihood of quitting the behavioral indicator of resiliency to distress[17], which is a validated game-like test designed to generate frustration and encourage the player to quit[8]. Adolescents with one long (L) and one short (S) variant of the *5-HTTLPR* polymorphism and poor family relations had a 12-14 time increased risk for high alcohol intoxication frequency[18]. If family relations were poor, the SS genotype had higher alcohol consumption than the LL genotype. The investigators suggest a possible heterosis, or increased functioning of the hybrid genotype, in cases in which the environment is unfavorable to adaptive functioning. The investigators did not, however, distinguish between high- and low-expressing L alleles, which may have contributed greatly to overall findings. Gerra *et al*[19] found a significantly positive association of S-allele-carrier genotypes with irritability levels and related temperamental traits in adolescents. One large longitudinal study examined 4334 seven-year-old children and found no significant relationships between the *5-HTTLPR* genotype and emotional symptoms in children, but those in the *5-HTTLPR* low expression group demonstrated an increase in the risk for emotional symptoms when faced with minimal to moderate stress[20]. These findings suggest that environmental effects need to be taken into account in elucidate the role of the *5-HTTLPR* polymorphism in pediatric emotion dysregulation.

The S and the low-expressing L allele may also have a negative impact on stress reactivity and tolerance due to their positive correlations with prolonged cortisol secretion following a stressor[21]. Even though the bulk of research on the *5-HTTLPR* polymorphism and related factors in children and adolescents is considered preliminary, serotonin-related mechanisms have paved the way for novel treatment modalities relating to other biological systems that may have an impact on serotonin levels. For example, recent research on omega-3 fatty acids has been linked to a depletion in docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) during early development, which may cause lower levels of serotonin and thereby incite a series of deleterious effects of mood dysregulation and stress reactivity, among other symptoms[22]. While SSRIs have been used to treat mood dysregulation in children and adolescents for several years now, management of DHA and EPA levels is a novel therapeutic option. Learning more about mechanisms of serotonin regulation and manipulation within the brain can facilitate the development of more effective medication and treatment

plans.

OTHER GENETIC POLMORPHISMS IMPLICATED IN EMOTION DYSREGULATION

While the bulk of pediatric research on genetic factors involved in emotion dysregulation focuses on serotonin, a number of other loci may also have an impact. A functional single-nucleotide polymorphism in the catechol-O-methyltransferase (*COMT*) gene encodes a valine to methionine mutation at position 158 (Val158Met) rs4680 in the enzyme that degrades dopamine[23]. The Val variant has higher activity of catabolizing dopamine than the Met variant. Prior evidence has shown that the *COMT* Met allele is associated with more severe emotion dysregulation in children and adolescents[24-26]. One study on 277 children and adolescents found that the Val allele carriers were more likely become irritable when their expected rewards are delayed, compared to their peers carrying no Val alleles[27]. These results suggest that the role of *COMT* (Val158Met) polymorphisms in mood regulation may be complicated, as the relationship between dopaminergic tone and mood regulation may be non-linear.

The dopamine receptor D2 (DRD2)/ankyrin repeat and kinase domain containing one polymorphism are other genetic variants associated with D2 dopamine receptor binding affinity that may also play a role in emotion dysregulation[28]. In a study of 65 children, the DRD2 Taq A1 allele was found to be associated with a greater sensitivity and emotionality to negative feedback, while simultaneously diminishing one's sensitivity to positive feedback[28]. The same study also found that children with the short allele (S) for the *5-HTTLPR* gene might show greater sensitivity to error processing in event-related potential experiments. Significantly enhanced early error-related negativity and later occurring error-related positivity were associated with the S-allele group compared to the homozygous L-allele group; such electrophysiological signals are thought to reflect the anterior cingulate activity[28].

Other genetic variants associated with mood dysregulation have been reported by preclinical and clinical studies primarily focused on adults. The role of these variants in pediatric mood dysregulation also deserves some attention. For example, adult carriers of the monoamine oxidase-A (MAOA) promoter variant associated with a lower gene expression may have a higher propensity for aggression and impulsivity, compared with carriers of the MAOA promoter variant associated with a higher gene expression[29,30]. Individuals with low-expression MAOA variant may have reduced left middle frontal gyrus activation and left amygdala and posterior thalamic activation in response to an anger trigger, compared to the control[31].

Another genetic variant that may be of importance involves the cAMP response element-binding protein (CREB)-regulated transcription coactivator 1 (CRTC1), a CREB protein coactivator of the brain-derived neurotrophic factor (BDNF) implicated in rodent models of depression[32]. One fMRI study of children found that a single nucleotide polymorphism (T/C) near the *CREB* gene might be associated with neural correlate for emotion reactivity-greater activation in the TT group, compared to the CC group, in the right dorsal anterior cingulate cortex, right putamen, right caudate nucleus and left anterior temporal pole, when the brain activity under a transient state of sadness[33]. Mice lacking the coactivator have a series of negative traits, including impulsive aggressiveness, social withdrawal, and increased emotional response to stressful events[34]. Mice without the *CRTC1* gene also demonstrate a reduced efficiency in serotonin and dopamine cycling in prefrontal cortex, as well as a decreased expression of susceptibility genes involved with neuroplasticity, including BDNF, providing a strong suggestion that the coactivator might play an important role in gene expression related to mood disorders. The L-type voltage-dependent calcium channel, alpha 1C subunit (*CACNA1C*) gene[35,36] is linked to mood disorders from different populations. The calcium channel may also be linked to the arousal system[37,38]. The calcium influx in the arousal system is modulated by glutamate[39] and Y-aminobutyric acid (GABA)[40]. The relationship between glutamate metabolism genes and mood disorders may be difficult to determine partly because such genes may be expressed in different brain regions. Research in these areas is essential to further understanding of psychiatric symptom etiology in children and adolescents.

DISCUSSION

There has been significant emerging evidence for the contribution of genetic variants to pediatric emotion dysregulation, thanks to the advances of genomic technologies. However, most of these genetic findings are challenged with the failure of replication across different populations, and hence genetic determinants of emotion dysregulation remain elusive. Inconsistent findings might continue to be a norm rather than an exception without taking into consideration the factors, such as genetic heterogeneity, clinical heterogeneity, and epigenetic phenomena associated with environmental influences. Current knowledge of genetic mechanisms underlying emotion regulation has been primarily based on research on adults, and hence more efforts to study the genetic basis for emotion regulation in children and adolescents are warranted. Some genetic variants (*e.g., COMT* polymorphisms) have been found to exert paradoxical effects on emotion dysregulation in children, which may be partly attributable to a non-linear relationship between variants and neurochemical

changes and environmental influences (*e.g.*, attachment). Additionally, the developing brain in the youth may further complicate genomic studies, as phenotypic features may fluctuate by age. For example, age-dependent changes in neural substrates related empathy have been observed in individuals with autism spectrum disorders or typically-developing individuals[41]. Additionally, autonomic arousal was uniquely heightened in adolescents[42]. Furthermore, activities of prefrontal regions in response to emotions are also age-dependent[43]. Finally, there are various psychological tasks related to emotion regulation associated with different brain circuits, and hence literature searches may be limited due to the heterogeneous contexts and terminologies. Nevertheless, the genetic component of emotion dysregulation constitutes an initial step of understanding the etiology of emotion dysregulation, but knowledge of hereditary and hormonal influences may yield robust improvements in pharmacological and therapeutic treatments that can benefit children and adolescents in managing dysfunctional emotional behaviors.

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ORIGINAL ARTICLE

Retrospective Study

Associative stigma in family members of psychotic patients in Flanders: An exploratory study

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Data sharing: Technical appendix, statistical code, and dataset available from the corresponding author at kirstencatthoor@yahoo.com. Participants did not give informed consent for data sharing at the time of the interviews.
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Abstract

AIM: To assess presence and severity of associative stigma in family members of psychotic patients and factors for higher associative stigma.

METHODS: Standardized semi-structured interview of 150 family members of psychotic patients receiving full time treatment. This study on associative stigma in family members of psychotic patients was part of a larger research program on the burden of the family, using "Interview for the Burden of the Family" and the chapters stigma, treatment and attribution from the "Family interview Schedule". The respondents were relatives, one per patient, either partner or parent. The patients had been diagnosed with schizophrenia or schizo-affective disorder. All contacts with patients and relatives were in Dutch. Relatives were deemed suitable to participate in this research if they saw the patient at least once a week. Recruitment took place in a standardized way: after obtaining the patient's consent, the relatives were approached to participate. The results were analyzed using SPSS Version 18.0.

RESULTS: The prevalence of associative stigma in this sample is 86%. Feelings of depression in the majority of family members are prominent. Twenty-one point three percent experienced guilt more or less frequent, while shame was less pronounced. Also, 18.6% of all

respondents indicated that they tried to hide the illness of their family member for others regularly or more. Three six point seven percent really kept secret about it in certain circumstances and 29.3% made efforts to explain what the situation or psychiatric condition of their family member really is like. Factors with marked significance towards higher associative stigma are a worsened relationship between the patient and the family member, conduct problems to family members, the patients' residence in a residential care setting, and hereditary attributional factors like genetic hereditability and character. The level of associative stigma has significantly been predicted by the burden of aggressive disruptions to family housemates of the psychotic patient.

CONCLUSION: Family members of psychotic patients in Flanders experience higher associative stigma compared to previous international research. Disruptive behavior by the patient towards in-housing family members is the most accurate predictor of higher associative stigma.

Key words: Associative stigma; Risk factors for higher stigma; Family members; Psychotic patients; Burden

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Core tip: Associative stigma is an extension of psychiatric stigma to those who care for patients, like family members. Scientific evidence on associative stigma in family members of psychotic patients is abundant, but culturally determined. This study tried to study the presence and severity of associative stigma in family members of psychotic patients in Flanders (Belgium) and evaluate factors to delineate subgroups vulnerable for higher associative stigma. The results show that associative stigmatization is a marked problem for parents and partners of psychotic patients: it is higher than so far demonstrated in previous international research. Disruptive behavior by the patient towards in-housing family members is the most accurate predictor of higher associative stigma. A better understanding of this complex phenomenon is certainly warranted, in order to perform more adequate clinical interventions towards family members of psychotic patients, to lower this destructive burden.

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INTRODUCTION

Stigma is defined as a discrediting and disgracing mark[1-5] usually leading to negative behavior for its bearer[6-10]. Different approaches have been used to conceptualize psychiatric stigma[1-5]. The definition and conceptualization of psychiatric stigma are still in full evolution. Aspects of devaluation, discrimination, decreased self-esteem, self-restricted behavior, and dysfunctional coping are almost always mentioned[1-4]. Most studies have consistently reported that patients with psychotic disorders[8-14], affective disorders[14], and alcohol dependence[14] experience stigmatization as a serious hindrance in daily life.

Associative stigma does not refer to the patients themselves, but is an extension of psychiatric stigma to those who care for patients, such as family members[15-24] and mental health care workers[6,7]. Subjective feelings of associative stigma are solely caused by the relationship with another stigmatized individual[15-18,20-24]. It is considered to be an important source of mental burden[19-24]. Marked stress, shame and blame, diminished self-worth, depression, anxiety and avoidance of social contacts are often mentioned. Multiple factors may contribute to the substantial associative stigma of family members[17], although there is evidence that some somatic diseases induce the same kind of stigma[18]. There is, for example, the widespread public assumption that bad parenting skills trigger mental illness. Besides, genetic models emphasize biological vulnerability and inheritance. And last but not least is the fact that family members are often blamed for non-compliance and thus relapse in the patient.

Research has shown that associative stigma appears to be greater in family members who have mental health problems themselves, whereas there is doubt if the diagnosis of the patient is of any significance[20,24]. In addition, there is substantial evidence that family members with higher socio-economic status show higher levels of stigma compared with others[8,15]. Several studies focusing on psychotic disorders demonstrated that a higher level of subjective stigma in family members is related with illness-related symptomatic behavior[15], a higher degree of positive symptoms[8], and male gender[17]. Half of the family members of psychotic patients use concealment about their relatives' psychiatric condition[15], and that a longer duration of illness is also associated with a higher degree of stigma[8,25].

Although evidence in literature is not conclusive, the abovementioned findings strongly indicate a stigmatizing effect of the diagnosis of a psychotic disease on family members of the patient. It should also be emphasized that family interactions and caregiver burden[26] are strongly influenced by cultural factors (widespread beliefs about the origin of disease, like demon possessions in Africa and patients' or family's misconduct in China). As previous studies on this topic investigated North-American[15,24], Chinese[8], Swedish[20] and African populations[19,22], it is worth questioning whether these effects are present in a Belgian sample too. The goals of the current study

Table 1 Socio-demographic data of patient and respondent, and schematic representation of the patient's case history *n* = 150 (%)

Diagnosis	
Schizophrenia/schizo-affective disorder	129 (86.0)/21 (14.0)
Treatment	
Inpatient/outpatient	81 (54.0)/69 (46.0)
Gender of patient	
Male/female	103 (68.7)/47 (31.3)
Average age of patient (SD)	33 yr (8.7 yr)
Gender of respondent	
Male/female	46 (30.7)/104 (69.3)
Relationship respondent/patient	
Parent/partner	118 (78.7)/32 (21.3)
Average age of respondent (SD)	56 yr (11.9 yr)
Education of respondent	
A-Level, FE or University/primary or GCSE (O-Level)	74 (49.3)/76 (50.7)
Total household income of respondent	
< €20K per annum/ > €20K per annum	122 (81.4)/28 (18.6)
Number of contact hours respondent/patient (SD)	5.4 h (1.8 h)
Duration of illness in years (SD)	9.1 yr (6.4 yr)
Number of times patient was taken into care (SD)	3.8 (3.2)
Psychopharmacological treatment	
With/without antipsychotic drugs	148 (98.6)/2 (1.4)
Behaviour	
Disorganised/not disorganised	132 (88.0)/18 (12.0)
Negative/not negative	44 (29.3)/106 (70.7)
Patient's place of residence	
At home/in institution	117 (78.0)/33 (22.0)

are two-fold: First we aim to determine the presence and severity of associative stigma in family members of psychotic patients in a Belgian sample. Second, we aim to exploratively determine factors that could help to delineate subgroups vulnerable for high levels of associative stigma, based on those factors that already have been suggested in previous studies.

MATERIALS AND METHODS

Participants

The respondents were relatives, one per patient at his or her own suggestion, either partner or parent. The patients had been diagnosed with schizophrenia or schizo-affective disorder (DSM-Ⅳ, TR, American Psychiatric Association)[27], according to SCID[28]. All patients were receiving full-time treatment, either in a day centre or as an outpatient in the University Centre in Kortenberg or the Night Hospital of Sint-Alexius in Elsene (Table 1), both in the Flemish part of the country. All contacts with patients and relatives were in Dutch. Relatives were deemed suitable to participate in this research if they saw the patient at least once a week. Recruitment of family members took place in a standardized way: after obtaining the patient's consent, the case psychiatrist would request relatives to participate in research about the burden of care of relatives of psychotic patients. Patients were selected in a third-line, university centre and respondents were only included if the patient gave permission. It should be taken into account that patients from a stigma-sensible environment could refuse to participate in this study. The declaration of Helsinki was followed during the whole procedure of the study.

Conceptualization

This study on associative stigma in family members of psychotic patients was part of a larger research program on the burden of the family[29]. Therefore, the interview consisted in several different parts. First we used the complete set of items pertinent to "Interview for the Burden of the Family"[30]. Additionally we went through the chapters stigma, treatment and attribution from the "Family interview Schedule", which in fact was part of a World Health Organisation study (WHO, 1992) on course and outcome of schizophrenia, that were already included in the Burden of the Family interview. For details on the questionnaire, we refer to Sartorius *et al*[31]. We interviewed relatives of 150 patients. The average duration of the interview was 105 min. The duration of patient's illness was operationalised as the number of years they had been ill since they had first been taken into psychiatric care.

Measures

Assessment of stigma: The sum total of all scores from the stigma chapter (Likert-scale from 0 to 3) determined the total stigma, with a minimum of 0 and a maximum of 42[31]. Because data are homogeneous, means and standard deviations are added in the result section. The presence of just one positive answer on the stigma questionnaire was enough to represent a form of perceived stigma[22].

Statistical analysis

The data were analysed using the Statistical Package for Social Sciences, version 18.0 (SPSS Inc., Chicago, IL). Patients and respondents were characterized with descriptive statistics to differentiate on associative stigma.

The Kruskal Wallis test (outcome measure = *P*-value) was chosen as a conservative non-parametric method because the distribution of the data was not-normal. It was used to assess differences in mean stigma score (continuous dependent variable) between groups. Categorical dependent group variables were factors we found in the literature: the relationship between the patient and the interviewed family member, the evolution in time of this relationship, disruptive behavior of the patient, treatment in inpatient or outpatient unit, disruptive eruptions towards family members, the patient's residence, attribution of the disease to heredity, character of biological brain problems, and contact between the interviewee and a mental health professional.

A multiple regression analysis (method = backward) was conducted in order to investigate the predictive

Table 2 Complete results of stigmatization questionnaire, ordered by item *n* = 150 (%)

	Never	Sometimes	Regularly	Often
Concerned about the neighbours	121 (80.7)	20 (13.3)	5 (3.3)	4 (2.7)
Concerned about people discovering what is going on	106 (70.7)	33 (22.0)	4 (2.6)	7 (4.7)
Tendency to conceal	89 (59.3)	38 (25.3)	11 (7.3)	12 (8.0)
Explanation about the situation	71 (47.3)	60 (40.0)	13 (8.7)	6 (4.0)
Secrecy	95 (63.3)	32 (21.3)	6 (4.0)	17 (11.3)
Concerned about being avoided or ignored	136 (90.7)	11 (7.3)	1 (0.7)	2 (1.3)
Explanation of the illness	106 (70.7)	26 (17.3)	11 (7.3)	7 (4.7)
Concerned about being accused	129 (86.0)	13 (8.7)	5 (3.3)	3 (2.0)
Concerned about a hesitation to marry	122 (81.3)	15 (10.0)	7 (4.7)	6 (4.0)
Concerned about leaving the house	120 (80.0)	24 (16.0)	3 (2.0)	3 (2.0)
Shame	129 (86.0)	19 (12.7)	0 (0.0)	2 (1.3)
Contact with other families	103 (68.7)	34 (22.7)	6 (4.0)	7 (4.6)
Feeling depressed or sad	55 (36.7)	44 (29.3)	25 (16.7)	26 (17.3)
Guilt	118 (78.7)	22 (14.7)	7 (4.6)	3 (2.0)

value of several variables on the level of stigma experienced by family members of psychotic patients. Level of stigma was entered as the dependent variable. Predictors (independent variables) were patient characteristics (diagnosis, gender, age, duration of illness, number of hospital admissions and relation between patient and respondent), socio-economic status of the respondent (educational background of family member and family income) illness related symptomatic behavior (positive symptoms: hallucinations and paranoia, disruption experienced by co-housing family members) contact with a mental health professional and biological attribution of illness (inheritability and bad biological functioning). Outcome measures are standardized β, *t*-values with p-values to indicate significance, with $\alpha \leqslant 0.05$ no correction for multiple testing due to interdependecy of the variables. Dummy variables were computed for nominal data.

Biostatistical review was performed after peer review by Luykx J.

RESULTS

Patients and respondents

The data of patients and respondents are shown in Table 1. Mean age of the participating patients was 33 with a male preponderance (male/female ratio: 103/47). There were more female participating relatives (mean age was 56), probably because most of them were parents. This disequilibrium between the number of male and female patients and respondents is a bias in the study. Patients were mostly diagnosed with schizophrenia, showed a relatively long illness course and were already taken several times into psychiatric care.

Level of associative stigma

The average total sum of all subjective stigmatization experienced by the family members was 6.0 (± SD 5.6), with scores ranging from 0 to 30. The complete set of results of the stigmatization questionnaire is shown in Table 2. If 1 positive answer on the questionnaire is considered as the experiencing of at least some kind of associative stigma (Shibre, 2001), the prevalence of associative stigma is 86% in the current sample.

At the individual item level, the most important finding of the study are feelings of depression being present in the majority of respondents (63.3%). More than 1 in 5 (21.3%) experienced guilt more or less frequent, while shame was less frequent (14%). Also, 18.6% of all respondents indicated that they tried to hide the illness of their family member for others regularly or more. Thirty-six point seven percent really kept secret about it in certain circumstances and 29.3% made efforts to explain what the situation or psychiatric condition of their family member really is like. Twenty percent was concerned about how and when the patient could leave the house. What is striking is that more than 10% of the respondents indicate to experience almost all items "sometimes" (except "concerned about being avoided or ignored" and "concerned about being accused").

Vulnerable subgroups

Table 3 shows the significant differences in the subjective experience of stigmatization as suffered by all respondents, taking into account the patient- and respondent-specific variables. The Kruskal Wallis Test revealed that all independent variables showed at least marginally significant differences in subjective feelings of stigma. Factors with marked significance towards higher associative stigma are a worsened relationship towards the family member (mean total stigma score 8.6 ± SD 1.1 *vs* 5.3 ± SD 0.5, $P = 0.003$), conduct problems to family members (mean total stigma score 9.6 ± SD 1.5 *vs* 5.5 ± SD 0.5, $P = 0.004$), the patients' residence in a residential care setting (mean total stigma score 8.9 ± SD 1.1 *vs* 5.3 ± SD 0.5, $P = 0.001$), and hereditary attributional factors like genetic hereditability (mean total stigma score 7.4 ± SD 0.7 *vs* 4.8 ± SD 0.5, $P = 0.006$) and character (mean total

Table 3 Differences in subjective stigmatization experience taking into account patient- and respondent-specific variables with the relevant *P*-value

Patient- and respondent-specific variables	Stigmatization-score (± SD)	*P*-value
Relation		
Parent/partner	6.4 (± 0.5)/4.9 (± 1.1)	0.030
Evolution of relation		
Worse/not worse	8.6 (± 1.1)/5.3 (± 0.5)	0.003
Disruptive		
Yes/no	8.1 (± 1.1)/5.7 (± 0.5)	0.020
Nature of patient		
Inpatient/outpatient	6.8 (± 0.6)/5.3 (± 0.7)	0.043
Disruption to family members		
Yes/no	9.6 (± 1.5)/5.5 (± 0.5)	0.004
Patient's residence		
Institution/at home	8.9 (± 1.1)/5.3 (± 0.5)	0.001
Attribution to heredity		
Yes/no	7.4 (± 0.7)/4.8 (± 0.5)	0.006
Attribution to character		
Yes/no	7.4 (± 0.7)/4.8 (± 0.5)	0.008
Attribution to biological brain problem		
Yes/no	7.1 (± 0.8)/5.6 (± 0.6)	0.050
Contact with psychotherapist		
Yes/no	6.8 (± 0.6)/4.5 (± 0.5)	0.060

stigma score 7.4 ± SD 0.7 *vs* 4.8 ± SD 0.5, $P = 0.008$). It is also worth mentioning that contact with a mental professional lead to a tendency of higher associative stigma (mean total stigma score 6.8 ± SD 0.6 *vs* 4.5 ± SD 0.5, $P = 0.06$).

Predictive factors

As Table 4 presents, the level of associative stigma has significantly been predicted by the burden of aggressive disruptions to family housemates of the psychotic patient ($\beta = 0.223$, $t = 2.074$, $P = 0.041$). The higher the burden of family members living together with the patient, the higher the level of associative stigma in the responding relative. The predictive capacity of hallucinations ($\beta = 0.204$, $t = 1.827$, $P = 0.072$) and the attribution of psychotic illness to inheritability ($\beta = 0.190$, $t = 1.716$, $P = 0.090$) correspond with a tendency towards statistical significance ($P = 0.05$-0.1) but were not significant.

DISCUSSION

This quantitative study into experiences of associative stigma in relatives of psychotic patients aimed to assess previously internationally reported presence and severity of associative stigma in a large Flemish sample, and tried to determine factors that could help to predict higher subjective associative stigma in the current cohort. Flemish parents or partners of adult patients receiving treatment for schizophrenia or schizo-affective disorder reported levels of associative stigma that are higher compared to other similar studies.

Table 4 Predictors of stigma experienced by family members of psychotic patients (n = 89)

	β	*t*	*P*-value
Constant		0.999	0.321
Gender of patient	0.072	0.648	0.519
Relation with patient	0.025	0.194	0.847
Education of family member	-0.013	-0.11	0.913
Age of patient	-0.238	-1.595	0.115
Number of years of illness	0.109	0.714	0.477
Number of hospital admissions	-0.033	-0.26	0.796
Positive psychotic symptom: hallucinations	0.204	1.827	0.072
Positive psychotic symptom: paranoia	0.134	1.283	0.203
Burden by housemates	0.223	2.074	0.041
Family income	0.062	0.526	0.601
Spoken to therapist	0.173	1.578	0.119
Biological background of illness: inheritability	0.19	1.716	0.09
Biological background of illness: bad biological functioning	0.005	0.044	0.965

Footnote: $R^2 = 0.25$.

Presence and severity of associative stigma

Regarding the presence and severity of associative stigma in our sample, an average total subjective stigma of 6 was observed; compared to a possible maximum score of 42, this score did not seem very pronounced. However, 86% of our respondents gave 1 or more positive answers on the questionnaire and thus experienced at least some sort of associative stigma. Note that Shibre *et al*[22] came to 75% of "stigmatized" relatives in Ethiopia, using the same questionnaire and scoring. In our cohort, a significant majority of respondents (63.3%) appeared to feel "episodically depressed or sad", which is substantially more than the 40% in Ostmann and Kjellin's study[20]. This study, comparable to ours with a semi structured interview, also asked family members directly about their own mental health problems as a result of the mental illness of their relative. In China[8], only 28% of relatives think that stigmatization has a mild to severe negative influence on healthy family members; it should be mentioned that in this country, the development of schizophrenia is attributed to totally different cultural contents, and the family is more responsible for the behavior of its members. Although we emphasize that all studies had different study designs and methods, and that study results are not easily generalizable, our data confirm the international findings on the extent of associative stigma, and even indicate that family members of psychotic patients in Flanders experience still higher levels of stigma as compared with previous research.

The finding that parents exhibited a greater level of subjective stigmatization in comparison to partners can be linked to the parents' assumption that they at least partially originated the emergence of the illness and have to deal with the associated sadness and sorrow of their child. Besides, they might experience

the demand for continuity of care and the underlying sense of responsibility. We suggest that the higher stigmatization level in relatives who attribute the psychotic disorder to hereditary factors and consider it as a "genetic" phenomenon confirms this hypothesis. Contact with a mental health professional resulted in a marginally significant increase in stigmatization, which is difficult to understand. It could be that respondents are more likely to approach a therapist because of their increased stigmatization experience. Conversely, they could also feel that approaching a professional might reflect badly on them. Ostmann and Kjellin[20] interpret this feeling of inferiority towards the psychotherapist as the most important luxating factor of this phenomenon. The absence of a significant correlation between the diagnosis of the patient (schizophrenia *vs* schizo-affective disorder) and the total subjective stigma is in line with results of previous research[15,20].

Predictive factors

The experience of disruptive behavior by in-housing family members of the psychotic patient was the most accurate predictor of higher associative stigma in family members of psychotic patients. The importance of positive and disease-related symptoms has already been mentioned in previous studies[8,15], and it is not surprising that disruption directed towards own family members is one of the most shocking and shaming experiences a relative can imagine. The interviewed relatives did not suffer solely, but also their closest family members had to deal with the patient's unpredictability and outbursts. The possibility of blame for incompetence to stop this acting out, and the fear of being avoided by others, leads to even more burden, diminished self-esteem and inevitably also more stigma. For mental health professionals, the knowledge of violent disruptions in the family environment of a psychotic patient, should be a warning signal for associative stigma and offers a chance to discuss it with the family members involved.

Respondents claimed that contact with outsiders was not problematic, but similarly they exhibited a marked tendency to conceal or explain their situation. Relatives also denied feelings of guilt or shame but at the same time they confirmed that they felt depressed. There is thus a marked difference between what relatives say and do on the one hand and the way they think and feel on the other hand. These discrepancies between the results at the individual item-level could point to an interaction between feelings of stigmatization and previously existing emotional, cognitive and even psychopathological phenomena. This makes us assume that relatives are not aware of the effect of stigmatization on their subjective burden experience as they often deny feelings of stigmatization. It is unclear whether this phenomenon could be explained in terms of shame, *i.e.*, an internalized fear that inhibits recognizing the stigmatization, or whether relatives no longer recognize the difference between the experience of stigma and the need to deny it. To explain these apparent contradictions, it might be useful to redefine associative stigma, or at least broaden the concept. The subjective stigmatization experiences in relatives of psychotic patients should be understood as a complex concept, in which negative cognitions, dissociative mechanisms, fear, shame and partial denial all play an important role. We also would like to refer to substantial similarities with the concept of self stigma, and its paradoxes, as described by Corrigan *et al*[32]. Recognizing stigmatization in itself already appears to have a stigmatizing effect, which often leads to a denial of this feeling.

The results of our research give a clear picture of the subjective stigmatization experience in relatives of psychotic patients in Flanders, Belgium. Although there is an increasing interest in literature to emphasize positive aspects in caregiving for psychotic patients by family members[33], we would like to highlight the importance of more fundamental research into the nature of stigmatization in different populations of patients, relatives and even professionals, in order to perform more adequate interventions to lower this destructive phenomenon.

Limitations and strengths

Our study is limited because of a selection bias: patients were selected in a third-line, university centre and respondents were only included if the patient gave permission. It should be taken into account that patients from a stigma-sensible environment could refuse to participate in this study. Besides that, there was disequilibrium between the number of male and female patients and respondents, and there were only parents and partners included, no children of patients. The current study's strengths are the large study cohort, and the possibility to compare results to previous international research.

In conclusion, the current study clearly demonstrates a high prevalence of substantial feelings of associative stigma in family members of psychotic patients in Flanders, Belgium. Factors with marked significance towards higher associative stigma are a worsened relationship between the patient and the family member, conduct problems to family members, the patients' residence in a residential care setting, and hereditary attributional factors like genetic hereditability and character. The experience of disruptive behavior by in-housing family members of the psychotic patient was the most accurate predictor of higher associative stigma. A better understanding of this complex and multidimensional phenomenon, and integration into daily patient care and family interventions is certainly warranted.

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cooperation in this study.

COMMENTS

Background

Stigma is defined as a discrediting or disgracing mark, usually leading to negative behavior on the part of its bearer. Different approaches have been used to conceptualize psychiatric stigma, and are still evolving. Aspects such as devaluation, discrimination, decreased self-esteem, self-restricted behavior, and dysfunctional coping are almost always mentioned. Associative stigma is an extension of psychiatric stigma to those who care for patients, such as family members and mental healthcare workers. Associative stigma in family members is determined by cultural, psycho-social and personal factors from patient as well as from family member.

Research frontiers

Scientific data on associative stigma among family members of psychiatric patients differ substantially, depending on patient- and relative characteristics. Given the current world wide treatment paradigm shifts, from inpatient to outpatient, it is important to better understand the mental burden and stigma experiences of family members of patients, in order to provide better clinical support and advice.

Innovations and breakthroughs

Flemish parents or partners of adult patients receiving treatment for schizophrenia or schizo-affective disorder report levels of associative stigma that are higher compared to other similar international studies. Factors with marked significance towards higher associative stigma are a worsened relationship between the patient and the family member, conduct problems to family members, the patients' residence in a residential care setting, and hereditary attributional factors like genetic hereditability and character. The experience of disruptive behavior by in-housing family members of the psychotic patient was the most accurate predictor of higher associative stigma.

Applications

This study highlights the importance of more fundamental research into the nature of stigmatization in different populations of patients, relatives and even professionals, in order to perform more adequate clinical interventions to lower this destructive phenomenon, given the current treatment paradigm shifts towards more outpatient treatment in the natural environment of the patient.

Terminology

Associative stigma is an extension of psychiatric stigma to those who care for patients, such as family members and mental healthcare workers. Coping mechanisms are conscious psychological adaptations to environmental stress, in order to obtain more comfort.

Peer-review

It is a well designed and correctly conducted survey. The topic is important and the results are interesting.

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ORIGINAL ARTICLE

Retrospective Study

Mood Spectrum Model: Evidence reconsidered in the light of DSM-5

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Abstract

AIM: to investigate studies conducted with the Mood Spectrum Structured Interviews and Self-Report versions (SCI-MOODS and MOODS-SR).

METHODS: We conducted a review of studies published between 1997 and August 2014. The search was performed using Pubmed and PsycINFO databases. Analysis of the papers followed the inclusion and exclusion criteria recommended by the PRISMA Guidelines, namely: (1) articles that presented a combination of at least two terms, "SCI-MOODS" [all fields] or "MOODS-SR" [all fields] or "mood spectrum" [all fields]; (2) manuscript in English; (3) original articles; and (4) prospective or retrospective original studies (analytical or descriptive), experimental or quasi-experimental studies. Exclusion criteria were: (1) other study designs (case reports, case series, and reviews); (2) non-original studies including editorials, book reviews and letters to the editor; and (3) studies not specifically designed and focused on SCI-MOODS or MOODS-SR.

RESULTS: The search retrieved 43 papers, including 5 reviews of literature or methodological papers, and 1 case report. After analyzing their titles and abstracts, according to the eligibility criteria, 6 were excluded and 37 were chosen and included. The SCI-MOODS and the MOODS-SR have been tested in published studies involving 52 different samples across 4 countries (Italy, United States, Spain and Japan). The proposed mood spectrum approach has demonstrated its usefulness mainly in 3 different areas: (1) Patients with the so-called "pure" unipolar depression that might manifest hypomanic atypical and/or sub-threshold aspects systematically detectable with the mood questionnaire; (2) Spectrum features not detected by other instruments are clinically relevant, because they might manifest in waves during the lifespan, sometimes together, sometimes alone, sometimes reaching the severity for a full-blown disorder, sometimes interfering with

other mental disorders or complicating the course of somatic diseases; and (3) Higher scores on the MOODS-SR factors assessing "psychomotor disturbances", "mixed instability" and "suicidality" delineate subtypes of patients characterized by the more severe forms of mood disorders, the higher risk for psychotic symptoms, and the lower quality of life after the remission of the full-blown-episode.

CONCLUSION: The mood spectrum model help researchers and clinicians in the systematic assessment of those areas of psychopathology that are still neglected by the Diagnostic and Statistical Manual of Mental Disorders 5 classification.

Key words: Mood disorders; Dimensional; Categorical; Unipolar; Spectrum; Bipolar; Diagnostic and Statistical Manual of Mental Disorders 5

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Core tip: Data emerging from the proposed mood spectrum approach suggest the existence of a continuum from "pure mania" to "pure depression", without a clear cut-off between the two realms. As a whole, the experience with the mood spectrum model enforces past and recent claims towards the need for a unitary dimensional approach to mood disorders.

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INTRODUCTION

The boundaries of mood disorders have expanded during the last two decades as a consequence of the growing interest in the atypical, subclinical and/or sub-threshold forms of unipolar and bipolar disorders[1,2]. Efforts were initially devoted to the identification of atypical and sub-threshold forms of depression (Depressive Spectrum)[3,4]. Subsequently, the manic/hypomanic side was explored[1,5,6] giving a new impulse to the literature on mood disorders in general.

An enlargement of the manic dimension of mood disorders was thus proposed, aiming to identify those bipolar syndromes that, not fitting in the classic categorical description of Diagnostic and Statistical Manual of Mental Disorders (DSM), have led to an over-diagnosis of "pure" unipolar forms[7]. However, the unipolar/bipolar dichotomy was still maintained as nuclear to all the proposed theoretic constructs.

At the beginning of the 90's, in an attempt to define "soft indicators of bipolarity", the focus was shifted on affective temperaments[8]. Over the following years, clinicians and researchers of the University of Pisa, Italy, and of the Universities of Pittsburgh, Columbia (New York) and California (San Diego), promoted the "Spectrum Project Collaborative Group" (SPCG) whose aim was to create and validate instruments able to recognize the wide halo of phenomenology surrounding the "core" features of each DSM mood category and overcome the classic unipolar/bipolar dichotomy[9].

The SPCG research agenda was based upon the empirical observation that a wide range of signs and features not included in the DSM might run completely overlooked or simply be considered not relevant from a clinical point of view. Conversely, a growing body of evidence indicated the clinical relevance of sub-threshold or atypical presentations of mood disorders and the potential usefulness of a dimensional assessment[9].

The SPCG proposed that life-long sub-threshold mood dysregulations represented the constitutional foundation of both full-blown manic and depressive episodes. The "SCI-MOODS" and the "its self-report version" (MOODS-SR) were developed to assess this wide area of phenomenology. The SCI-MOODS was the first version of the questionnaire, the MOODS-SR being its self-report version. The same authors constructed a MOODS-SR last-month version. All the versions were developed in parallel in English and Italian with a back translation and a subsequent validation for internal consistency and inter-rater reliability. The instruments consisted of 161 items coded as present or absent for one or more periods of at least 3-5 d through the subject's lifetime or over the past week or month[10]. The MOODS-SR was originally composed of four domains: (1) The Neurovegetative domain, assessing disturbances and rhythmic changes in feelings, eating attitudes, sexual activity and sleep, including rhythmic variations in affective and sub-affective symptoms; (2) the Energy levels domain, assessing changes in everyday activities, with special attention devoted to work, hobbies and social life; (3) the mood Domain, exploring the whole realm of depressive and manic symptoms, signs and sub-threshold manifestations of mood dysregulations; and (4) The cognitive domain, assessing changes in the cognitive realm that occur together with mood dysregulations[11].

The potential implications and the conceptual and methodological advantages of the proposed mood spectrum model have been already described[9-12]. However, at that time, evidence from clinical studies using the SCI-MOODS and the MOODS-SR was limited. The aim of this paper is to review and summarize the studies conducted with the SCI-MOODS and the MOODS-SR over the past 15 years and reconsider the evidence in the light of the DSM-5.

MATERIALS AND METHODS

We conducted a review of studies published between

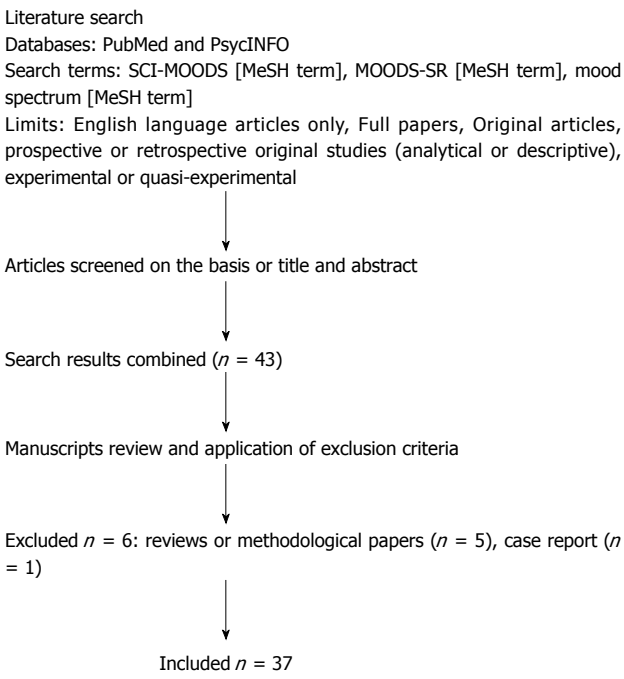

Figure 1 Flow diagram of study selection. SCI-MOODS: Mood Spectrum Structured Interview; MOODS-SR: MOODS Spectrum self-report version.

1997 (year of the first publication regarding the proposed mood spectrum approach) and August 2014. The search was performed using Pubmed and PsycINFO databases. Analysis of the articles followed inclusion and exclusion criteria derived from the ones recommended by the PRISMA Guidelines[13]. We included the following: (1) articles that presented a combination of at least two terms, namely "SCI-MOODS" [all fields] or "MOODS-SR" [all fields] or "mood spectrum" [all fields]; (2) manuscript in English; (3) original articles; and (4) prospective or retrospective original studies (analytical or descriptive), experimental or quasi-experimental. Exclusion criteria were as follows: (1) other study designs, such as case reports, case series, and reviews; (2) non-original studies including editorials, book reviews and letters to the editor; and (3) studies not specifically designed and focused on SCI-MOODS or MOODS-SR.

We utilized a flow diagram (Figure 1) to summarize the total number of screened papers and the number of those included in the review process, as suggested by the PRISMA Guidelines[13]. No extraction forms for the data extraction process were used, mainly because the studies on the proposed mood spectrum model were conducted in different fields and with different aims, as described in detail in the paragraphs of the result section. Two authors completed a formal training in reviewing data and performing meta-analyses, independently from this manuscript (AC and MGM).

Initially, the search retrieved 43 papers, including 5 reviews of literature or methodological papers, and 1 case report. After analyzing their titles and abstracts, according to the eligibility criteria, 6 were excluded and 37 were chosen and included in the final sample (Figure 1).

Statistical analysis

No new data have been added in this paper. No new analyses or meta-analyses were performed. The description of statistical methods used in any study can be found in the related papers.

RESULTS

The SCI-MOODS and the MOODS-SR have been tested in published studies involving 52 samples across 4 countries (Italy, United States, Spain and Japan) (see Table 1).

The SCI-MOODS and the MOODS-SR: Validity and reliability

The first two studies with the SCI-MOODS tested its validity and reliability. The reliability of the interview was proved to be excellent: the inter-rater reliability of domains ranged between 0.93 and 0.94, and the internal consistency of domains ranged between 0.79 and 0.92. In terms of discriminant validity, patients with mood disorders had significantly higher total and MOODS domain scores than controls, and patients with a bipolar disorder scored significantly higher on the manic component than patients with unipolar depression[10,14]. Subsequently, the self-report version of the questionnaire, the MOODS-SR, was developed and validated[11]. The results of the validation study were partially replicated by Ghouse *et al*[15]. Berrocal *et al*[16] validated a Spanish version of the MOODS-SR. A Swedish version of the questionnaire is currently undergoing the validation process.

A second step was the attempt to give the MOODS-SR a post-hoc structure with a factor analysis. The aim of the factor analysis was to determine, with a statistical approach, factors able to differentiate the pure dimensions of the depressive and the manic realm. The first study focused on the factor structure of mania-hypomania. The MOODS-SR was administered to a sample of 617 patients with a bipolar I disorder, diagnosed with the SCID-I. A classical exploratory factor analysis, based on a tetra choric matrix, was carried out on the 68 items of the manic/hypomanic component, followed by an Item Response Theory (IRT)-based factor analytic approach and by an IRT-based bi-factor analysis. Five factors of the manic/hypomanic component were identified: "Psychomotor Activation", "Mixed Instability", "Spirituality/Mysticism/Psychoticism", "Mixed Irritability" and "Euphoria". This approach permitted to subtype two clinical phenotypes of mania: the "pure mania", characterized by typical, atypical and sub-threshold symptoms of euphoria and psychomotor activation, and the "mixed mania", characterized by instability and irritability[17]. In a second study, the clinical features of 598 patients

Table 1 Mood Spectrum Structured Interview and Mood Spectrum Self-Report version studies

Ref.	Subjects	Design	Diagnostic criteria	Instruments	Results
Fagiolini *et al*[10]	491 (141 students, 116 gastrointestinal pts, 112 pts with BPD, 122 pts with recurrent MDEs)	Validation study (Italy)	DSM-IV	SCID-I, SCI-MOODS	Good discriminant validity and internal consistency
Dell'Osso *et al*[11]	41 (21 pts with MDEs or BPD *vs* 20 controls)	Validation study (Italy)	DSM-IV	SCID-I, SCI-MOODS, MOODS-SR	Good reliability of the self-report version (MOODS-SR) of the SCI-MOODS. Intraclass correlation coefficients ranged from 0.88 to 0.97
Veltri *et al*[34]	91 pts with TMD *vs* 26 TMD-free subjects	Open study (Italy)		Helkimo's Clinical Dysfunction Index (CDI), MOODS-SR	Total scores of depressive domains significantly higher in moderate or severe dysfunctional than in TMD-free and mild dysfunctional pts
Cassano *et al*[18]	213 (117 pts with recurrent MDEs in remission and 106 pts with BP-I)	Open study (Italy)	DSM-IV	MINI, SCI-MOODS	Patients with recurrent UP depression endorsed a substantial number of manic/hypomanic symptoms over their lifetimes
Manfredini *et al*[35]	85 subjects (34 bruxers *vs* 51 non-bruxers)	Open Study (Italy)	DSM-IV	MOODS-SR, PAS-SR	Significant differences between bruxers and controls emerged for the presence of both depressive and manic symptoms in MOODS-SR
Manfredini *et al*[36]	131 subjects screened for temporomandibular disorder (TMD)	Open study (Italy)	DSM-IV	MOODS-SR, PAS-SR, assessment for TMD	Significantly higher prevalence of both mood and panic-agoraphobic symptoms in myofascial pain pts than in the other diagnostic groups (TMD-free, disc displacement and joint disorders)
Manfredini *et al*[37]	20 pts with myofascial pain, 18 pts with temporomandibular joint pain-TMJ, 22 pts with combined pain *vs* 25 pts with non-painful TMD *vs* 29 TMD-free subjects	Open study (Italy)	DSM-IV	MOODS-SR, PAS-SR, assessment for TMD	Patients with painful TMD scored significantly higher than comparison groups in all MOODS-SR depressive domains
Cassano *et al*[19]	39 pts with Borderline PD + BPD *vs* 21 pts with Borderline PD	Open study (Italy)	DSM-IV	SCID-I, MOODS-SR, SCID-II	Lifetime manic-hypomanic mood dysregulations correlated with psychotic spectrum features in borderline patients
Benvenuti *et al*[45]	103 (70 pts with BP-I, 24 pts with BP-II, 4 pts with SA, 5 pts with BPD-NOS	Open study (United States)	DSM-IV	SCID-I, MOODS-SR, W-SAS, PAS-SR	WSAS scores on current depressive, manic, and panic spectrum total scores showed a highly significant "depressive spectrum" effect
Dell'Osso *et al*[30]	92 pts with Rheumatoid Arthritis	Open study (Italy)	DSM-IV	HAQ, MOS-SF36, MOODS-SR	Lifetime mood depressive spectrum was related with impaired HRQoL levels
Manfredini *et al*[38]	105 controls with bruxing behaviors	Open study (Italy)	DSM-IV	MOODS-SR	Prevalence of mood psychopathology was significantly higher in bruxers. Significant differences between bruxers and non-bruxers emerged in total MOODS-SR scores
Koukopoulos *et al*[57]	24 pts with Unipolar Depression *vs* 15 pts with BP-II	Open study (Japan)	DSM-IV	SCI-MOODS	Patients with BP-II disorder tended to show apparently quick disappearance of depressive symptoms
Ghouse *et al*[15]	71 (49 with MDEs or BPD or GAD, 22 controls)	Validation study (Spanish)	DSM-IV	SCID-I, BDI, MOODS-SR, Clinician-Administered Rating Scale for Mania	MOODS-SR good internal consistency and test-retest reliability. Significant positive correlations between depressive sub-domains and BDI and between manic-hypomanic subdomains and CARS for Mania
Piccinni *et al*[32]	92 pts with Rheumatoid Arthritis	Open study (Italy)	DSM-IV	MOS-SF36, MOODS-SR, PAS-SR	Significant worsening of all MOS SF-36 scores related to higher scores of the depressive domains of MOODS-SR
Benvenuti *et al*[20]	90 (25 pts with Borderline PD, 16 pts with BPD, 19 pts with MDE, 30 controls)	Open study (Spanish)	DSM-IV	SCID-I, MOODS-SR	No statistical significance for any (sub) domain considered between patients with BPD and Bipolar Disorder
Manfredini *et al*[39]	47 subjects (17 pts with BPD, 14 pts with MDEs, 16 controls)	Open study (Italy)	DSM-IV	SCID-I, SCI-MOODS-SR	Allopregnanolone/progesterone levels correlate with mixed features
Berrocal *et al*[16]	598 pts with MDE	Open study (Italy + United States)	DSM-IV	SCID-I, MOODS-SR	Central role of depressed mood, psychomotor retardation and suicidality. The factors "Drug/Illness related depression", "Psychotic features" and the neurovegetative dysregulation were identified

Cassano *et al*[17]	617 pts with BPD	Open study (Italy + United States)	DSM-IV	SCID-I, MOODS-SR	9 factors initially identified, 5 of them (Psychomotor Activation, Mixed Instability, Spirituality/Mysticism/Psychoticism, Mixed Irritability, Euphoria) subsequently retained
Dell'Osso *et al*[27]	130 (65 pts with PTSD *vs* 65 controls)	Open study (Italy)	DSM-IV	SCID-I, MOODS-SR	Statistically significant and positive associations were found between the presence of manic/hypomanic and depressive symptoms and the likelihood of suicidal ideation or attempts
Dell'Osso *et al*[29]	167 pts with fibromyalgia	Open study (Italy)	DSM-IV	SCID-I, MOS-SF36, FIQ, MOODS-SR	A high rate of lifetime manic symptoms was related to the Pain Visual Analogic Scale of the FIQ and the FIQ total scores and to the "bodily pain", and to the physical and mental component scores of the MOS SF-36
Mauri *et al*[41]	316 pts with MDEs	Depression Phenotype Study: Randomized (Italy + United States)	DSM-IV	SCID-I, MOODS-SR, HAM-D	In patients who reached remission from an MDE according to the Hamilton Rating Scale for Depression, scores on the depressive component of the MOODS-SR predicted relapses in the subsequent 6 mo
Benazzi *et al*[51]	222 pts with MDEs	Depression Phenotype Study: Randomized (Italy + United States)	DSM-IV	SCID-I, MOODS-SR	Association between the manic/hypomanic component of the MOODS-SR and the polymorphisms of the 5-HTTLPR was moderated by gender
Miniati *et al*[42]	312 pts with MEDs (78 with a history of emotional/physical abuse, EPA)	Depression Phenotype Study: Randomized (Italy + United States)	DSM-IV	SCID-I, SCID-II, HRSD, QIDS, MOODS-SR	Patients with a history of EPA did not differ from those without on HAM-D scores at baseline. The two groups differed on factors: "dep. Mood", "psychomotor retardation", "drug and illness-related depression", and "neurovegetative symptoms"
Frank *et al*[44]	226 pts with MDEs	Depression Phenotype Study: Randomized (Italy + United States)	DSM-IV	SCID-I, HAM-D, Q-LES-Q, WSAS, MOODS-SR, PAS-SR	Poor quality of life associated with the MOODS-SR factors "depressive mood" and "psychotic features" and the PAS-SR factors "separation anxiety" and "loss sensitivity". Functional impairment was associated with the MOODS-SR factor "psychomotor retardation" and the PAS-SR factor "fear of losing control"
Dell'Osso *et al*[28]	48 (25 pts with PTSD *vs* 23 controls)	Open study (Italy)	DSM-IV	SCID-I, IES, MOODS-SR	PTSD pts showed a significant decrease in TSPO density. TSPO density correlated with the number of lifetime manic/hypomanic spectrum symptoms
Bazzichi *et al*[31]	110 (60 pts with fibromyalgia *vs* 50 pts with Rheumatoid Arthritis)	Open study (Italy)	DSM-IV	MOODS-SR (OTHERS?)	FM pts showed significantly higher scores than RA patients in "mood depressive", "cognition depressive" domains and in total depressive component
Miniati *et al*[43]	318 pts with MDEs	Depression Phenotype Study: Randomized (Italy + United States)	DSM-IV	SCID-I, HAM-D, MOODS-SR, PAS-SR, SHY-SR	Participants with lower scores on the MOODS-SR "psychomotor activation" factor experienced more rapid remission with SSRI
Fagiolini *et al*[46]	291 pts with MDEs	Depression Phenotype Study: Randomized (Italy + United States)	DSM-IV	SCID-I, SCID-II, HRSD, QIDS, MOODS-SR	Compared to low scorers, participants with high scores on the LPR factor had greater severity of depression and more bipolarity indicators
Dell'Osso *et al*[24]	103 (53 pts with complicated grief *vs* 50 controls)	Open study (Italy)	DSM-IV	SCID-I, ICG, ASA-27, W-SAS, MOODS-SR	Patients with CG reported significantly higher scores on the MOODS-SR, ASA-27, and WSAS with respect to controls. The scores on the ASA-27 were significantly associated with the MOODS-SR depressive and manic components
Apfelbaum *et al*[22]	50 pts with complicated grief	Open study (Italy)	DSM-IV	SCID-I, ICG, MOODS-SR	MOODS-SR depressive and rhythmicity/vegetative items were associated with increased suicidal ideation and attempts, while sub-threshold manic items with suicidal ideation
Rucci *et al*[52]	1158 pts with MDEs or BPD	Open study (Italy + United States)	DSM-IV	SCID-I, MOODS-SR	MOODS-SR psychomotor activation factor identified subgroups with an increasing likelihood of bipolar disorder diagnosis
Dell'Osso *et al*[25]	116 (66 pts with PTSD, 22 pts with complicated grief, 28 pts with PTSD+complicated grief)	Open study (Italy)		SCID-I, ICG, ASA-27, W-SAS, MOODS-SR	Patients with CG+PTSD or PTSD alone reported significantly higher scores on the manic component of the MOODS-SR

Dell'Osso *et al*[23]	389 subjects (156 with Mood Disorders, 54 pts with Panic Disorder, 79 pts with schizophrenia, 100 controls)	Open study (Italy)	DSM-Ⅳ-TR	BPRS, OBS-SR, MOODS-SR, SCID-I	Sexual obsessions more frequent in schizophrenia (54.4%), followed by mood disorders (35.9%), and independently associated with all aspects of suicidal behaviors
Hardoy *et al*[40]	1066 pregnant women	Prospective Study (Italy)	DSM-Ⅳ	SCID-I, EPDS, MOODS-SR	The prevalence of suicidality in women who had MmD during pregnancy was 26.4% and 34.1%, assessed with the MOODS-SR and the EPDS, respectively, while it was 18.4% (MOODS-SR) and 30.6% (EPDS) during the postpartum period
Berrocal *et al*[21]	63 pts with MDE, BPD, Cluster B PD, comorbid BPD and PD-B	Open Study (United States)	DSM-Ⅳ	MINI and SCID II, MOODS-SR, BI, TEMPS-A and IPDE	BD+PD-B pts showed a more severe type of emotional dysregulation. Patients with BD+PD-B comorbidity had an earlier onset and more severity in suicide attempts, hospitalizations and self-harm behaviors
Dell'Osso *et al*[26]	475 students	Open study (Italy)	DSM-Ⅳ	MOODS-SR, TALS-SR (Others?)	Significantly higher MOODS-SR domain scores were found in PTSD survivors compared to those without. The mood depressive, cognition depressive and energy manic MOODS-SR domains were associated with an increased likelihood of PTSD
Rucci *et al*[14]	139 (52 pts with BP-I, 32 pts with BP-II, 17 pts with BPD-NOS *vs* 38 controls)	Open Study (United States)	DSM-Ⅳ	MOODS-SR, SCID-I, GAF	BPD pts scored significantly higher than controls on the total MOODS-SR scores and all sub-domains. Comparisons across BD subtypes revealed statistically significant higher scores among BD I, BD II and BD NOS only for the total MOOD-SR scores and for mood mania and energy domains

SCID-I: Structured Clinical Interview for DSM Disorders (Axis I Disorders); SCID-II: Structured Clinical Interview for DSM Disorders (Axis II Disorders); SCI-MOODS: Structured Clinical Interview for the Mood Spectrum; MOODS-SR: Structured Clinical Interview for the Mood Spectrum (self report version); PAS-SR: Structured Clincal Interview for the Panic-Agoraphobic Spectrum (self report version); WSAS: Work and Social adjustment scale; HAQ: Health Assessment Questionnaire; MOS-SF36: Medical Outcome Study-Short form 36; CDI: Helkimo's Clinical Dysfunction Index; MINI: Mini International Neuropsychiatry Interview; BDI: Beck Depression Inventory; FIQ: Fibromyalgia Impact Questionnaire; HAM-D: Hamilton Rating Scale for Depression; QIDS: Quick Inventory for Depressive Symptomatology; Q-LES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire; IES: Impact Event Scale; SHY-SR: Structured Clinical Interview for the Social Phobic Spectrum (self-report version); CGI: Clinical Global Impression; ASA-27: Adult Separation Anxiety (27 items); BPRS: Brief Psychiatric Rating Scale; OBS-SR: Structured Clinical Interview for the Obsessive-Compulsive Spectrum (self report version); EPDS: Edinburgh post-natal depression scale; BI: Bipolarity Index of Gary Sachs; TEMPS-A: Temperament Evaluation of Memphis-Pisa-Paris and San Diego (self-questionnaire version); IPDE: Identify, predict, decide and execute; TALS-SR: Structured Clinical Interview for the Post-traumatic stress spectrum (self report version); GAF: Global Assessment of functioning; TMD: Temporomandibular disorder.

with unipolar depression (UP) were assessed with the MOOD-SR lifetime version. In this case too, a classical exploratory factor analysis using tetra choric correlation coefficients and an IRT-based factor analysis approach were adopted to analyze the data on 74 items of the instrument that explore cognitive, mood and energy/activity features associated with depression. The factor analysis identified three factors describing the core aspects of depression ("depressive mood", "psychomotor retardation" and "suicidality") and 3 more factors: the "neuro-vegetative symptoms", the "Drug/Illness related depression" and the "psychotic features" factors[18].

The detection of the lifetime manic/hypomanic component in patients with "pure" unipolar depression

One of the aims behind the construction of the MOODS-SR was to create an instrument able to recognize soft and atypical manic/hypomanic features both in bipolar and unipolar patients. As originally hypothesized, the instrument identified mild hypomanic features among 117 patients with a DSM-Ⅳ diagnosis of remitted recurrent unipolar depression and 106 patients with a bipolar I disorder. The number of manic/hypomanic items endorsed was directly related to the number of depressive items in both diagnostic groups. A more important presence of the manic/hypomanic component was found among those patients who had a wider number of depressive symptoms through their lifetime. This direct correlation was somehow surprising for patients with the so-called "pure unipolar" form of depression. Moreover, the number of sub-threshold manic/hypomanic items was related to an increased likelihood of endorsing paranoid and delusional thoughts and/or suicidal ideation among patients who were diagnosed as affected by "pure" unipolar depression, according to the DSM-IV categorical approach[19].

The detection of lifetime mood spectrum signs and symptoms among patients with other DSM-IV diagnoses and/or somatic/physical conditions

Benvenuti *et al*[20] assessed patients with borderline personality disorder with and without a comorbid mood disorder. The depressive and the manic-hypomanic component of the mood spectrum were higher than in normal controls and significantly correlated with the presence of sub-threshold psychotic symptoms, as assessed with the the Structured Clinical Interview for the Psychotic Spectrum (SCI-PSY) also in those patients who did not meet criteria for a DSM-5 diagnosis for a mood disorder[20]. Patients with borderline personality disorder and a comorbid mood disorder showed an even stricter correlation between the manic/hypomanic component of the MOODS-SR and different domains and sub-domains of the SCI-PSY[20]. These results were partially replicated by Berrocal *et al*[21], in a following study with the Spanish version of the questionnaire[21]. In a more recent paper Apfelbaum *et al*[22] tested the MOODS-SR in patients with Bipolar disorders with and without a comorbid Cluster B personality disorder. The results of the study showed that patients with BD + PD-B comorbidity had an earlier onset and more severity in suicide attempts, hospitalizations and self-harm behaviors[22].

More recently Apfelbaum *et al*[22] and Dell'Osso *et al*[23-25] has explored the role of mood dysregulations in patients with complicated grief (CG) and/or Post Traumatic Stress Disorder (PTSD) without full-blown mood disorders[22-25]. The aims of these studies were to better characterize patients in the perspective of a more tailored treatment approach, and to identify vulnerability towards CG and PTSD. Patients were assessed with the MOODS-SR lifetime version. MOODS-SR scores were higher in patients with CG than in controls. Patients with CG in comorbidity with PTSD and patients with PTSD reported significantly higher scores on the manic component of the MOODS-SR than patients with CG alone[26,27]. Patients with PTSD and higher MOODS-SR scores showed a higher likelihood of suicidal ideation or attempts[28]. In a following study, the same research group tested the 18 kDa mitochondrial translocator protein (TSPO) density in a sample of patients with a non-war-related PTSD. The decrease of TSPO correlated with the manic/hypomanic component of the mood spectrum, suggesting a possible role of sub-threshold bipolar comorbidity in PTSD-related neurobiological dysregulations[29]. These studies proved the ability of the MOODS-SR to detect sub-threshold manic/hypomanic signs in psychiatric patients without a full-blown diagnosis of Bipolar Disorder. The manic/hypomanic dimension as assessed with the MOODS-SR was associated with greater severity, higher risk for a psychotic evolution and higher suicidal risk in patients without a mood disorder.

The MOODS-SR has proved its usefulness also in medical settings and in non-psychiatric samples. Patients with fibromyalgia showed a relationship between the MOODS-SR lifetime manic spectrum scores, severity of pain and health-related quality of life[30]. Not surprisingly, lifetime depressive spectrum symptoms negatively affected quality of life in patients with rheumatoid arthritis (RA) while sub-threshold manic features improved the subjective perception of health[31,32]. Sub-threshold depressive symptoms were over-represented in fibromyalgic patients as compared to RA patients[33,34]. The mood spectrum instruments were also utilized to detect subthreshold mood dysregulations among patients with temporo-mandibular disorders or bruxism[35-39]. Hardoy *et al*[40] tested the instrument among subjects during the premenstrual phase showing that mixed features correlate with levels of allopregnanolone and progesterone.

Mauri *et al*[41] published a large study performed to assess suicidality in a non-clinical sample of 1066 subjects during the perinatal period and to report suicidality rates in women with major or minor depressive episode (MmD). Subjects were screened with the SCID, during the perinatal period and with the MOODS-SR. The period prevalence of suicidality was 6.9% (95%CI: 6.0-7.8) during pregnancy and 4.3% (95%CI: 3.4-5.2) during postpartum, assessed with the MOODS-SR, and was 12.0% (95%CI: 10.8-13.2) during pregnancy and 8.6% (95%CI: 7.4-9.8) during the postpartum period, assessed with the EPDS. The prevalence of suicidality in women who had MmD during pregnancy was 26.4% and 34.1%, assessed with the MOODS-SR and the EPDS, respectively, while it was 18.4% (MOODS-SR) and 30.6% (EPDS) during the postpartum period.

Sub-typing clinical phenotypes of Mood Disorders: The "Depression Phenotype Study"

The Depression phenotypes study was a multi-center study financed by NIMH grants (Grant number: MH65376; MH30915) and performed by the University of Pittsburgh and Pisa. Aim of the study was to identify the mediators and moderators of depression treatment outcomes. Patients with a non-psychotic major depressive episode were randomly assigned to a pharmacotherapeutic intervention (escitalopram) or to the Interpersonal Psychotherapy (IPT), an empirically validated manual-based treatment for major depression. If the initial treatment was not successful in bringing about remission (HAM-D < 7), subjects received the other treatment as add-on. Patients were administered several instruments including the MOODS-SR in its lifetime and last-month versions.

Miniati *et al*[42] showed that in patients who reached remission according to the Hamilton Rating Scale for Depression, scores on the depressive component of the MOODS-SR predicted relapses in the subsequent 6 mo. The same authors analyzed patients belonging to the

Depression phenotypes study with a history of emotional and physical abuse. The two groups differed on several mood spectrum factors, namely: "depressive mood", "psychomotor retardation", "drug and illness-related depression", and "neurovegetative symptoms"[43].

Patients with lower scores on the "psychomotor activation" factor of the MOODS-SR experienced a shorter time to remission when treated with SSRIs compared to IPT[43]. Subsequent analyses indicated that 7 of 9 (77.8%) patients who experienced hypomania during the study had psychomotor activation scores above the median (⩾ 5), suggesting that this factor might be useful for the identification of patients at high risk of switching[44].

Depressive mood, suicidality, psychomotor retardation, neurovegetative symptoms, and the psychotic features factors of the MOODS-SR resulted as non-specific predictors of longer time to remission when in monotherapy[44].

Benvenuti *et al*[45] assessed the quality of life and the functional impairment of those patients who reached remission in the above-mentioned sample. In a previous study Fagiolini *et al*[46] proved the usefulness of MOODS-SR in detecting depressive sub-threshold manifestations that cause functional impairment in a sample of patients with bipolar disorder in remission. Patients with unipolar depression showed a poorer quality of life associated with the MOODS-SR factors "depressive mood" and "psychotic features". Higher functional impairment was associated with the MOODS-SR factor "psychomotor retardation". These data confirmed the ability of the MOODS-SR in recognizing subtle signs and symptoms not detected by the usual rating scales (namely HAM-D), but which interfere with the subjective perception of quality of life and functioning.

These results confirmed the hypothesis that a better definition of clinical phenotypes should be a crucial factor in the decision-making process for more specific and effective treatment strategies for the so-called pure unipolar depression.

In a following study, the hypothesis that "retardation" could be at the same time an indicator of clinical severity of depression and a "validator" of a bipolar diathesis in unipolar patients was tested[47], in line with previous observations in this field[48-51].

Unipolar patients with higher scores on the lifetime psychomotor retardation factor of the MOODS-SR showed greater severity of depression and more bipolar indicators, namely: earlier age at onset, longer duration of illness, higher frequency of episodes, more lifetime suicide attempts and a positive family history of psychiatric disorders. These patients were also more likely to endorse sub-threshold bipolar features, as assessed by the MOODS-SR, such as "Mixed Irritability", "Mixed Instability" and "Creativity".

Starting from a neurobiological point of view, Rucci *et al*[52] analyzed the relationship between the polymorphisms of 5-HTTLPR genotype and the MOODS-SR manic-hypomanic component over the lifetime. The authors found that the association between the manic/hypomanic component of the MOODS-SR and the polymorphisms of the 5-HTTLPR was moderated by gender. Moreover, women with unipolar disorder and the "ss" genotype were characterized by a higher severity of depression[52].

The detection of subjects with the so-called "pure" Unipolar Depression who are at risk for a Bipolar Disorder: The Classification-Tree approach

An exploratory statistical approach based on a classification tree analysis was used with the aim to determine which combination of clinical, demographic, and psychopathological factors and corresponding cut-off scores could best discriminate patients with unipolar disorder from those with bipolar disorders. Data were extracted from a database of 1158 patients tested with the MOODS-SR in the United States and Italy between October 2001 and March 2008. Patients received a DSM-Ⅳ-TR diagnosis of unipolar or bipolar mood disorders as assessed with the SCID-I. The classification tree utilized 5 mania spectrum factors and 6 depression spectrum factors derived from the MOODS-SR in combination with demographic and clinical characteristics. The psychomotor activation factor, assessing the presence of thought acceleration, distractibility, hyperactivity and restlessness for 1 or more periods of at least 3 to 5 d in the lifetime, identified subgroups with an increasing likelihood of bipolar disorder diagnosis. Mixed instability and suicidality contributed to further sub-typing the sample into mutually exclusive groups, characterized by a different likelihood of a diagnosis of bipolar disorder. Only gender proved to be useful to improve the discrimination, among the overall set of demographic and clinical characteristics included in the analysis[53].

DISCUSSION

The MOODS-SR has demonstrated its usefulness in different fields. Patients with the so-called unipolar depression manifest hypomanic atypical and/or sub-threshold aspects that are detectable with the mood questionnaire. Spectrum features, as assessed with the MOODS-SR, might manifest in waves during the lifespan, presenting sometimes together, sometimes alone, sometimes reaching the severity for a full-blown disorder, sometimes interfering with other mental disorders or complicating the course of somatic diseases. Higher scores on the factors assessing psychomotor disturbances, mixed instability and suicidality delineate specific subtypes of patients characterized by a more severe form, a higher risk for psychotic symptoms, and a lower quality of life after remission.

Clinical observations have shown that psychomotor

activation and irritability characterized mixed depression in 33% to 47% of patients with mood disorders[54-56]. On the other hand, some of the DSM-5 mixed features are rarely present in mixed states[57]. As a whole, the new classification does not clarify the overlap between unipolar and bipolar depression[58]. The DSM-5 authors added a "mixed features" specifier in patients with manic, hypomanic and depressive episode, thus recognizing the importance of soft bipolar signs in depressive patients and the typical instability of these manifestations (symptoms have to be present "nearly" every day). This notwithstanding, DSM-5 considers as "mixed features" only those sub-threshold symptoms of depression and mania that do not overlap. This definition permits the inclusion of seven symptoms as representative of "mixed features". As a result, psychomotor agitation, irritability and distractibility have been excluded, leading to a clinical construct that does not fit the whole realm of clinical reality[57,59]. Our studies with the MOODS-SR performed on unipolar patients confirmed and highlighted the complexity of the mixed dimension. The whole realm of the manic/hypomanic manifestations could appear in patients with unipolar depression and their assessment during the entire lifetime is crucial for their definition.

As a whole, the experience with our instruments enforces past and recent claims towards the need for a dimensional approach to mood disorders[2,5,60,61].

Thus, data emerging from the mood spectrum approach suggest the existence of a continuum from "pure mania" to "pure depression", without a clear cut-off between the two realms, confirming the need for a probabilistic approach towards mood disorders[60,62].

Several observations already highlighted the need of a more refined assessment of the broader area of psychopathology surrounding the core features of mood disorders in a dimensional manner. For example, studies with the Multidimensional Assessment of Thymic States (MAThyS) focused on the processes of inhibition/activation in 5 different dimensions (emotional reactivity, cognition speed, psychomotor function, motivation and sensory perception)[63], while the TEMPS-A[64] assessed the classical Akiskal's affective temperaments[65,66]. Conversely, the DSM-5 task force for mood disorders decided that the unipolar/bipolar dichotomy would better fit for a diagnostic manual, which major aim is to help clinicians and researchers in the diagnostic process. The authors of the DSM-5 undoubtedly made an effort towards the "dimensional" realm, enlarging the too strictly designed categories of the DSM-Ⅳ, adding a number of subcategories and several specifiers for each diagnosis. The implementation of mood disorders with the "other specified" and "unspecified" categories represents an attempt to give clinical significance to atypical and sub-threshold manifestations of mood disorders. The description of previously neglected features (such as hopelessness) among the diagnostic criteria of depression moves in the same direction. This effort towards a more refined description of mood dimensions enlarged the number of subcategories (now 14) through a complex combination of coded courses and severity specifiers mimicking a dimensional rating.

As far as we know, the MOODS-SR is the only instrument exploring the "core" criterion diagnostic symptoms and their associated features, as well as the wide range of symptoms surrounding the typical features of mania and depression, in a unitary format. Findings suggest that the mood spectrum approach is able to offer clinicians a more clinically meaningful assessment of psychopathology than the established measures of manic and depressive severity. We propose the SCI-MOODS as an advance in clinical and research methodology. Unfortunately, even if the change in DSM-5 pointed-out for a more subtle definition of mood disorders a wide area of mood spectrum psychopathology is still neglected. The dimensional revolution in DSM-5 did not happen. Recalling Zenone's paradox, we can continuously reduce the distance between subcategories but we will never create a continuum. As a consequence a wide realm of psychopathology is still unexplored, unrecognized and not yet coded. The mood spectrum approach could help in the assessment of these neglected features by filling the DSM-5 gaps of the categorical approach.

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COMMENTS

Background

The "Mood Spectrum" model is here used to refer to the broad range of manifestations of a DSM 5 disorder from "core" symptoms to the sub-threshold and/or atypical signs. Spectrum manifestations may be present during, between, or even in the absence of, an episode of full-blown disorder. The authors have developed a structured clinical interview and a self-report version to assess the mood spectrum (SCI-MOODS, MOODS-SR) and to evaluate the whole range of depressive and manic symptoms along a "continuum" (unipolar/bipolar) model. The proposed spectrum model is complementary to the categorical approach of Diagnostic and Statistical Manual of Mental Disorders 5.

Research frontiers

The spectrum approach, complementing the Diagnostic and Statistical Manual of Mental Disorders 5, should help the clinician and the researcher in the identification of specific subgroup of patients more likely to respond to specific treatment approaches. Moreover, the goal is to provide an instrument useful for genetic and neuro-imaging researches targeted to specific clinical phenotypes of mood disorders.

Innovations and breakthroughs

Data emerging from the mood spectrum approach suggest the existence of a continuum from "pure mania" to "pure depression", without a clear cut-off between the two realms, confirming the need for a probabilistic approach towards mood disorders.

Applications

To better understand the clinical variability within the same DSM 5 category of patients; To systematically assess the presence of lifetime manic/hypomanic

symptoms among patients diagnosed as "pure" unipolar according to the categorical approach; To improve patient-therapist communication, using a systematic definition of the clinical phenotype of each patient; To better delineate the outcome measures; To improve the sub-typing of patients for research and treatment purposes.

Terminology

Mood Spectrum assessment is based on DSM criterion symptoms as a starting point, and extends the categorical description to encompass a halo of surrounding clinical phenomena, namely: associated features described in the DSM, atypical symptoms, maladaptive behavioral traits and temperamental features that do not appear in the DSM.

Peer-review

This is a well-conducted review of studies and the table is useful and informative. The manuscript including abstract is well written and structured clearly.

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ORIGINAL ARTICLE

Clinical Trials Study

Light treatment for seasonal Winter depression in African-American *vs* Caucasian outpatients

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Abstract

AIM: To compare adherence, response, and remission with light treatment in African-American and Caucasian patients with Seasonal Affective Disorder.

METHODS: Seventy-eight study participants, age

range 18-64 (51 African-Americans and 27 Caucasians) recruited from the Greater Baltimore Metropolitan area, with diagnoses of recurrent mood disorder with seasonal pattern, and confirmed by a Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders-Ⅳ, were enrolled in an open label study of daily bright light treatment. The trial lasted 6 wk with flexible dosing of light starting with 10000 lux bright light for 60 min daily in the morning. At the end of six weeks there were 65 completers. Three patients had Bipolar Ⅱ disorder and the remainder had Major depressive disorder. Outcome measures were remission (score ≤ 8) and response (50% reduction) in symptoms on the Structured Interview Guide for the Hamilton Rating Scale for Depression (SIGH-SAD) as well as symptomatic improvement on SIGH-SAD and Beck Depression Inventory-Ⅱ. Adherence was measured using participant daily log. Participant groups were compared using *t*-tests, chi square, linear and logistic regressions.

RESULTS: The study did not find any significant group difference between African-Americans and their Caucasian counterparts in adherence with light treatment as well as in symptomatic improvement. While symptomatic improvement and rate of treatment response were not different between the two groups, African-Americans, after adjustment for age, gender and adherence, achieved a significantly lower remission rate (African-Americans 46.3%; Caucasians 75%; P = 0.02).

CONCLUSION: This is the first study of light treatment in African-Americans, continuing our previous work reporting a similar frequency but a lower awareness of SAD and its treatment in African-Americans. Similar rates of adherence, symptomatic improvement and treatment response suggest that light treatment is a feasible, acceptable, and beneficial treatment for SAD in African-American patients. These results should lead to intensifying education initiatives to increase awareness of SAD and its treatment in African-American communities to increased SAD treatment engagement. In African-American *vs* Caucasian SAD patients a remission gap was identified, as reported before with antidepressant medications for non-seasonal depression, demanding sustained efforts to investigate and then address its causes.

Key words: Seasonal affective disorder; Depression; Light treatment; African-American; Black; Remission gap; Ethnicity; Race

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Core tip: Consistent findings suggesting that light treatment is safe and effective for Seasonal affective disorder (SAD) emerged from prior research on samples with highly predominant Caucasian representation. As there are no previous reports on light treatment for SAD in African-Americans, we undertook the first study comparing effects of light treatment in African-American and Caucasian patients with Seasonal Affective Disorder. After six weeks of treatment, improvement in depression scores, response (50% improvement in symptoms), and adherence to treatment were similar between the two racial groups. However, the remission rates were significantly lower in African-Americans. Thus additional research is needed to better understand and ultimately reduce the remission gap between Caucasian and African-American patients with SAD.

Uzoma HN, Reeves GM, Langenberg P, Khabazghazvini B, Balis TG, Johnson MA, Sleemi A, Scrandis DA, Zimmerman SA, Vaswani D, Nijjar GV, Cabassa J, Lapidus M, Rohan KJ, Postolache TT. Light treatment for seasonal Winter depression in African-American *vs* Caucasian outpatients. *World J Psychiatr* 2015; 5(1): 138-146 Available from: URL: http://www.wjgnet.com/2220-3206/full/v5/i1/138.htm DOI: http://dx.doi.org/10.5498/wjp.v5.i1.138

INTRODUCTION

Many species manifest behavioral and physiological changes in response to seasonal changes in day-length. Today, the effect of changes in daylength on humans may be smaller than in other animals because artificial lighting may blunt macro-environmental photoperiodicity. However, a sizable proportion of individuals manifest more pronounced seasonal changes, with some having major depression episodes in the fall and winter with spontaneous remission in spring and summer, defined as Seasonal Affective Disorder with winter pattern (SAD)[1]. Symptoms of SAD resemble seasonal changes in physiology and behavior in other photoperiodic mammals (including changes in appetite, weight, sleeping patterns, and patterns of social interactions). Light treatment is a safe and efficacious antidepressant intervention for SAD[1-4]. It may also prove to be a beneficial treatment for non-seasonal depression[4,5], as the mechanisms underlying the antidepressant action of bright light treatment overlap in part with those of antidepressant medications[6,7]. Although it appears that the prevalence of SAD in African-Americans is similar to the general population living at the same latitude[8], no previous study has focused on light treatment in African-Americans. Based on previously reported lower rates of adherence to antidepressants in African-American patients with non-seasonal depression[9,10], we hypothesized a lower adherence to light treatment, and a lower treatment response and remission in African-American patients when compared to Caucasian patients with SAD with winter pattern.

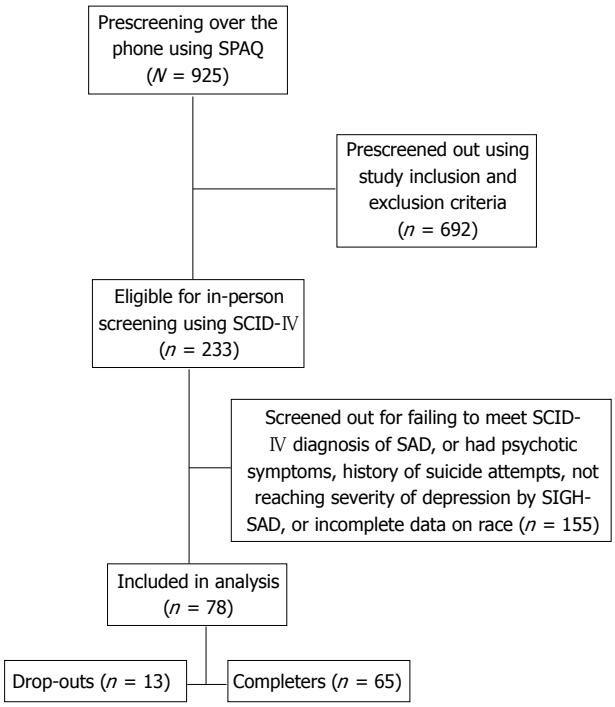

Figure 1 Flow chart showing number of participants from beginning to end of study. SPAQ: Seasonal pattern assessment questionnaire; *N*: Total sample at beginning of study; *n*: Population sample at various stages after initial screening; SCID-Ⅳ: Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-Ⅳ; SAD: Seasonal Affective Disorder; SIGH-SAD: Structured Interview Guide for the Hamilton rating scale-Seasonal Affective Disorder version.

MATERIALS AND METHODS

This was a six-week study primarily focused on prediction of remission and response following light treatment in African-American and Caucasian patients with Seasonal Affective disorder with Winter pattern. This study was an exploratory aim of an National Institute of Health-supported study (1R34MH073797-01A2). Recruitment took place over three consecutive Fall to Winter intervals, beginning in Fall 2007 and ending in Winter 2010. Approval for the study protocol was obtained from the Institutional Review Board of the University of Maryland.

Participants

Participants in this study were patients with SAD with Winter pattern, recruited from the larger Baltimore metropolitan area through posters, flyers, and local newspaper ads. Figure 1 is a flow chart showing numbers of participants involved in the study from the initial telephone screening to the end. Patients self-identified as African-Americans or Caucasians consistent with the methodology recommended by the National Research Council consensus document on race and ethnicity[11].

Seasonal pattern assessment questionnaire

Prescreening (screen #1) was conducted by phone using the Seasonal Pattern Assessment Questionnaire (SPAQ)[12]. This seventeen item psychometric instrument first designed by Rosenthal *et al*[12] has been widely used as a research instrument in the study of SAD. It has been shown to be an accurate screening instrument for identifying patients with SAD[13,14]. In one study by Magnusson, the SPAQ was shown to have sensitivity, specificity and positive predictive value for that group of 94%, 73% and 45%, respectively[15]. In another study, Young *et al*[16] reported that the SPAQ has good psychometric properties in terms of score distribution, test-retest reliability, internal consistency, factor structure and item-latent traits relationships. Several other studies have shown high sensitivity but low specificity for the SPAQ, thus making it a good screening but poor diagnostic tool. In our study, participants who received a SPAQ global seasonality score of 11 or greater, reported a Winter pattern, as well as reported being at least moderately affected in daily functioning were considered positive screen. These individuals were invited to attend an in-person screening, informed consent session and for evaluation of eligibility to participate in the study.

In-person screening (screen #2) was performed by trained clinicians completing the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (DSM)-Ⅳ Axis Ⅰ Disorders-Clinician Version (SCID-Clinician Version)[17].

Inclusion and exclusion criteria

Inclusion criteria for the study were: age 18-64; history of Major Depressive Disorder or Bipolar Ⅱ Disorder with seasonal pattern specifier, by DSM-Ⅳ, text revision and/or a score of 21 or greater on the Structured Interview Guide for Hamilton Rating Scale for Depression-SAD Version (SIGH-SAD)[18]. Eligible participants repeated the SIGH-SAD by phone interview 24 h prior to the first scheduled light session (screen #3), as well as on the morning of the first light session (screen #4). The participants had to demonstrate a consistent SIGH-SAD score of 21 or greater over 2 wk to be eligible for participation. Women of childbearing potential who were pregnant, nursing, or intending to become pregnant were excluded. Patients were also excluded if they used drugs or had history of alcohol abuse in the past year, if they met SCID criteria for Bipolar Ⅰ, Psychotic disorders, if they reported past suicide attempts or active current suicidal ideation; or if they worked night shift. Other exclusion criteria were human immunodeficiency virus infection, systemic lupus, myocardial infarction or stroke, advanced glaucoma, and self-report of sensitivity to bright light or vision problems that are uncorrectable by glasses (*e.g.*, if they answered negatively when queried as to whether they could distinguish colors or see stars at night). Treatment with antidepressants, mood stabilizers, or antipsychotic medications during the one month prior to screening, were also criteria for exclusion. After complete description of the study,

participants' understanding was evaluated using a research consent form booklet. Informed consent was obtained to show participants' agreement and voluntary enrolment in the study.

Light treatment

Treatment was performed using the Apollo BriteLITE 6 (Apollo, American fork, Utah) whose name has since changed to Phillips BriteLITE 6. (Phillips HealthCare, Andover MA, product HF 3310 http://www.usa.philips.com/c-p/HF3310_60/britelite-6-energy-light with dimensions of 7.1 cm × 11 cm × 17.4 cm in/18 cm × 28 cm × 44 cm), and a peak wavelength of 545 nm.

The first light treatment session was conducted at the General Clinical Research Center of the University of Maryland, and included teaching and reviewing the light treatment procedures with participants and assessing response to the initial treatment. The intensity of 10000 lux was verified during the first session with a light meter and was obtained consistently from a distance of 33 cm from the center of the light box to the eyes. To maintain the correct distance from the light box to the eye level, a string measuring 34 cm was tied just above the light box. Participants were instructed to check their distance by straightening the string from the light box to a midpoint between their eyes, just above the nose.

Participants completed home-based daily bright light therapy for 6 wk, and treatment beginning at 10000 lux for 60 min upon awakening[19].

Previous studies have shown that light therapy is generally most effective when administered earlier in the day[19-21], as early morning treatment advances circadian rhythms, which are often phase delayed in SAD patients[20,21]. Participants were also instructed to use a timer on the light box to automatically shut off treatment after the recommended time interval.

The protocol allowed for flexible duration of light exposure with weekly adjustment. Weekly assessments were completed by phone with trained clinicians to assess mood symptoms, adherence to light, side effects, and measures related to hunger and food craving. We decided against a fixed-dose treatment instead preferring a flexible administration to maximize response and adherence in a clinically plausible context. Duration of light treatment was increased by fifteen minutes daily for participants who did not have at least a 30% reduction in SIGH-SAD score at the end of week one, a 50% reduction in SIGH-SAD score at the end of week two, or did not fulfill remission criteria (SIGH-SAD score ⩽ 8) at the end of week three. Conversely, duration of treatment was decreased by fifteen minutes daily for any report of a side effect of 4 or greater on a 7-point Likert scale. The management of patients who showed poor response or side effects was discussed by a junior clinician with a senior psychiatrist with extensive experience with SAD and light treatment. The methodology used in our study was similar to a protocol used in recent clinical trials comparing light treatment to cognitive-behavioral therapy in patients with SAD[22].

Measures

Depression scores were assessed using two measures, one semi-structured interview, the SIGH-SAD[18], and a self report measure, the Beck Depression Inventory-Second Edition (BDI-Ⅱ)[23]. The primary outcome measure was the SIGH-SAD remission and response status, as defined above.

Adherence measurement

Participants were asked to complete a daily log reporting on the time and duration of light treatment used that day. Adherence logs were collected weekly by members of the research team and recorded. Adherence was defined as number of days in which light treatment was used as prescribed, and non-adherence defined as total number of days missed or not used as prescribed.

Statistical analysis

Descriptive measures include means and standard deviations for continuous variables and proportions and percents for categorical variables. Comparisons of the participants by race were made using *t*-tests for continuous variables (change from baseline for mood measures and adherence), and χ^2 tests for categorical variables. Multiple linear regression analysis was used to compare race sub-groups on changes in depression scores with adjustment for adherence, age, education, and gender. A sensitivity analysis for remission was performed including all participants who entered the study rather than just those who completed it. Four participants who did not receive treatment were also included. Assumptions for the sensitivity analysis were that: (1) If SIGH-SAD was ⩽ 8 (*i.e.,* remission) at week 6, then patient was considered in remission at the end of the study; (2) If SIGH-SAD data were missing at week 6, but the rating at week 4 was ⩽ 8, then patient was considered in remission at the end of the study; and (3) If data for both weeks 4 and 6 were missing, then patients were considered not in remission. For the sensitivity analysis of adherence, all patients were included. If data for one week were missing, we counted that as 7 d missed.

RESULTS

No differences were found between African-Americans and Caucasians in mean age, gender, marital status, or proportion of bipolar Ⅱ patients. The overall educational level was lower in African-Americans than Caucasians; specifically, a higher percentage of

Table 1 Characteristics of the participants in the two groups *n* (%)

Variable	African-Americans (n = 51)	Caucasians (n = 27)	P-value[1]
Age, yr, mean ± SD	43.1 (10.3)	47.0 (10.1)	0.11
Gender male	19 (37.3)	14 (51.9)	0.21
Bipolar Ⅱ diagnosis	2 (3.9)	1 (3.7)	0.96
Education: High school or less	26 (52.0)	7 (25.9)	0.03
Marital status			
Married or cohabiting	7 (14.0)	5 (18.5)	0.42
Widowed, divorced, or separated	12 (24.0)	11 (40.8)	0.19
Never married	31 (62.0)	11 (40.7)	0.15

[1]P-values from t-test comparing races on age; χ^2 for other variables.

Table 2 Comparison of pretreatment and post-treatment depression scores

Variable	African-Americans	Caucasians	P-value[1]
Pre-treatment mood scores	(n = 51)	(n = 27)	
SIGH-SAD, mean ± SD	33 (6.9)	31 (6.4)	0.22
BDI-Ⅱ, mean ± SD	25 (10.9)	23.6 (8.4)	0.58
Post-treatment mood scores	(n = 41)	(n = 24)	
SIGH-SAD, mean ± SD	9.31 (6.9)	6.79 (6.0)	0.15
BDI-Ⅱ, mean ± SD	9 (7.9)	7.3 (7.4)	0.41

[1]P-values from t-test compare the two groups on pre-treatment and post-treatment depression scores. SIGH-SAD: Structured Interview Guide for Hamilton-Seasonal Affective Disorder version; BDI-Ⅱ: Beck Depression Inventory Second Edition.

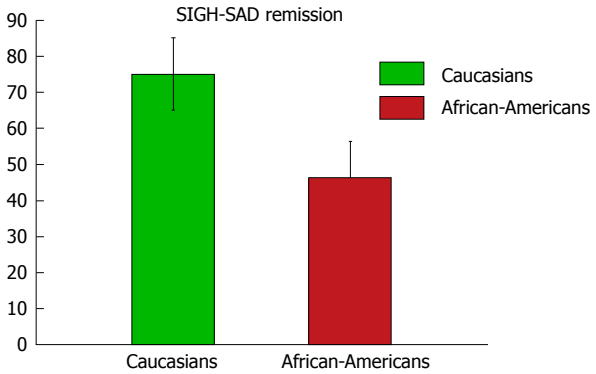

Figure 2 Graph comparing remission rates between the two groups. SIGH-SAD: Structured Interview Guide for the Hamilton rating scale-Seasonal Affective Disorder version.

African-Americans had a high school education or less (52% African-Americans *vs* 26% Caucasians, P = 0.03) as shown in Table 1. There were no differences in frequency of side effects or adverse reactions between the two groups, and none were rated severe.

In Table 2 we present a comparison between the two racial groups on pre-treatment and post-treatment depression scores using SIGH-SAD and BDI-Ⅱ. There was no statistical difference between average baseline and post-treatment depression scores between Caucasian and African-American patients.

Table 3 presents main outcome measures following 6 wk of light treatment. Although both race groups showed similar decreases in the SIGH-SAD and BDI-Ⅱ scores and similar post-treatment response rates, the proportion of remissions at post-treatment was significantly higher in Caucasians than in African-Americans (46% African-Americans *vs* 75% Caucasians, P = 0.02) (Figure 2). In a logistic regression model of remission at 6 wk adjusted for age, gender, education, and percent adherence, African-Americans were less likely to achieve remission than Caucasians (OR = 0.25; 95%CI: 0.08-0.81; P = 0.02). Table 3 also shows no group differences on adherence expressed as number of days missed or percent days adherence (equivalent measures). Adherence was 73% for African-Americans and 82% for Caucasians.

After linear regression adjustment for age, gender, education, and adherence, there were no significant differences in treatment related changes in depression scores between African-Americans and Caucasians. This is shown in Table 4.

Table 5 presents results of the intent-to-treat sample, including all those who were randomized. Based on the assumptions described in the Methods (see sensitivity analysis) for n = 78, in the logistic regression model of remission at 6 wk (adjusted for gender, percent adherence, and education) African-Americans were less likely to achieve remission than Caucasians (OR = 0.21, 95%CI: 0.07-0.66; P = 0.008). Those who were lost to follow up at 6 wk were compared with those with 6 wk data using χ^2 and t-test analyses. No significant race group differences were found for gender (P = 0.36), age (P = 0.96), baseline SIGH-SAD (P = 0.68), and baseline BDI-Ⅱ (P = 0.71). An ANCOVA model including race, gender, and age did not show significant difference between the groups in light exposure duration (F = 2.480; df = 1, 60; P = 0.12).

DISCUSSION

In this study, African-American participants with SAD had a lower remission rate than Caucasian participants following six weeks of light treatment, but there were no significant differences between the two race groups in adherence, average symptomatic

Table 3 Response, remission, and depression score changes by groups

Variable	African-Americans (n = 41)	Caucasians (n = 24)	P-value[1]
Response, 50% reduction SIGH-SAD, n (%)	33 (80.5)	20 (83.3)	0.78
Remission, SIGH-SAD < 8, n (%)	19 (46.3)	18 (75.0)	0.02
SIGH-SAD, % change, mean ± SD	-70.4 (22.7)	76.0 (22.6)	0.34
BDI-Ⅱ, % change, mean ± SD	-61.8 (32.2)	-68.1 (32.9)	0.46
POMS-A, % change, mean ± SD	-46.6 (46.7)	-46.8 (48.8)	0.98
POMS-D, % change, mean ± SD	-52.7 (47.1)	-49.2 (54.9)	0.78
Treatment days missed, mean ± SD	8.7 (11.0)	7.4 (8.3)	0.61
Percent adherence, mean ± SD	79.4 (26.2)	82.4 (19.7)	0.61

[1]P-values from t-test comparing races on age; χ^2 for other variables. SIGH-SAD: Structured Interview Guide for Hamilton-Seasonal Affective Disorder version; BDI-Ⅱ: Beck Depression Inventory Second Edition; POMS-A: Profile of Mood States-Anxiety; POMS-D: Profile of Mood States-Depression.

Table 4 Adjusted mean changes in depression score outcomes in African-Americans and Caucasians, adjusted for adherence, age, education and gender

Variable	African-Americans (n = 41)	Caucasians (n = 24)	P-value[1]
Mood scale			
SIGH-SAD	-22.9 (1.6)	-25.2 (2.1)	0.41
BDI-Ⅱ	-16.6 (2.0)	-16.4 (2.6)	0.95

[1]P value from linear regression. SIGH-SAD: Structured Interview Guide for Hamilton-Seasonal Affective Disorder version; BDI-Ⅱ: Beck Depression Inventory Second Edition.

improvement, and response rates. To our knowledge, this is the first study investigating differences between African-Americans and Caucasians in response to light treatment in SAD.

Racial differences for treatment response and remission have been previously reported with pharmacological treatment of non-seasonal depression. From the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, Lesser *et al*[24] reported that African-Americans had lower remission rates on the 17-item Hamilton Rating Scale for Depression and the 16-item Quick Inventory of Depressive Symptomatology-Self Report (18.6% and 22% respectively) compared to whites (30.1% and 36.1%). However, there was no statistically significant difference between races after adjusting for baseline socioeconomic, clinical, and demographic differences. In their analysis of DNA samples from the STAR*D trial, Binder et al. showed that a Single Nucleotide Polymorphism [single-nucleotide polymorphisms (SNP); rs 10473984] variation within the corticotrophin-releasing hormone binding protein locus appeared contributory to poor response and lower remission to treatment with citalopram in African-Americans and Hispanic patients[25]. In an earlier report from the STAR*D trial, McMahon *et al*[26] reported that the A allele of the SNP marker HTR2A which encodes for serotonin 2A receptor was over six times more frequent in white than in black participants and was responsible for better response to citalopram by white participants compared to blacks. Among many factors that may explain why certain outcomes such as adherence and response rates were similar in African-Americans and Caucasians in our study in contrast to significant racial differences reported in previous pharmacological trials, African-Americans may perceive light therapy as more acceptable and less stigmatizing than medications. This hypothesis was not formally tested.

In general, the response rate of 81% and remission rate of 52% reported in this study are somewhat more favorable compared to other studies on light treatment for SAD[3,20,21,27]. For instance, Lam *et al*[28] compared light treatment using 10000 lux bright light for 30 min daily with fluoxetine 20 mg orally daily for 8 wk. Their study showed no significant difference in clinical response rate, which was 67% for both groups, while remission rates were 50% for light therapy and 54% for fluoxetine.

We also note that there was no significant difference in adherence to daily light treatment between African-Americans and their Caucasian counterparts in our study. The adherence of 73% in African-Americans and 82% in Caucasians in our study is similar to the 83.3% found by Michalak *et al*[29], and it compares favorably with adherence to antidepressants[30]. When compared to antidepressants, light treatment has more benign side effects[28], potentially leading to higher adherence. Other side effects, such as precipitating hypomania and mania, are similar in light treatment and antidepressants[31]. Additionally, more rapid improvement with light treatment[28,32] may contribute to a better adherence with this non-pharmacological treatment.

The previously reported higher melanin content of the pupil and retinal pigment epithelium in African-Americans[33,34] may reduce the retinal illuminance in African-American SAD patients during light treatment. However, the magnitude of this effect is unclear, as is the effect of these reduced levels on remission.

Study limitations

Limitations of this study include an open label design, a

Table 5 Sensitivity analysis including all participants *n* (%)

	African-Americans (n = 51)	Caucasians (n = 27)	P-value[1]
Remission, SIGH-SAD ≤ 8	19 (37.3)	18 (66.7)	0.01
Treatment days missed, mean ± SD	11.3 (13.9)	7.4 (8.3)	0.13
Percent adherence, mean ± SD	73.2 (33.1)	82.4 (19.7)	0.13

[1]P-values from t-test comparing races on age; χ^2 for other variables. SIGH-SAD: Structured interview guide for the Hamilton-Seasonal Affective Disorder version.

limited sample size, and absence of objective markers of adherence. The recruitment method may have induced a selection bias that may have influenced favorably, but spuriously, the adherence rate.

We also did not collect information on number of lifetime depressive episodes or duration of current episode. The flexible dosing of treatment in our study, although representative of real world clinical practice, may have affected the outcomes. In addition, our generalizability may be limited as our inclusion and exclusion criteria may have led to selectively including a less severe subset of patients, having excluded patients with history of suicide attempts, current suicidal ideation, Bipolar 1 disorder, and comorbid substance abuse as well as patients on often used psychotropic medications. Including patients on psychotropic medications in the study, although increasing its generalizability, would have required unaffordably larger sample size and budget, to permit appropriate statistical adjustments.

This is the first study directly comparing light treatment outcome in two groups, African-American and Caucasian patients. A similar average degree of symptomatic improvement and adherence in African-Americans, combined with a previously reported lower awareness of SAD in this minority group[8] justify increasing psychoeducation outreach efforts regarding SAD and light treatment in that sub-sample of the population. However, there is a need to better understand the lower remission rate in African-Americans, similar to that of antidepressant medications. In the subset of patients who respond but do not achieve remission with light treatment, combination with antidepressant medication or cognitive behavioral therapy is currently advocated. Considering differences in pupil and retinal pigmentation in African-Americans it might be possible that specific protocols with distinct light intensity and wavelength could reduce the reported racial remission gap. This is particularly important, as complete remission with antidepressant treatment is the target for all treatment modalities for mood disorders, considering implications for health, functioning, and quality of life.

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COMMENTS

Background

The authors' prior research has suggested that Seasonal Affective Disorder (SAD) prevalence in African-Americans is similar to that of the general population living at similar altitude, and awareness of the disorder and its treatment is low among African-Americans. This study is the first to investigate effects of light treatment, generally considered a first-line treatment for SAD, in African-Americans as compared to Caucasian patients.

Research frontiers

Research in this area is moving towards identification of biological markers of prediction of response to light therapy, as well as combination of treatments and individualizing modalities and sequences of treatment.

Innovations and breakthroughs

Multiple areas of investigation have included investigating ways of administering light treatment (*e.g.*, dawn simulators), wavelength of treatment (lower wavelength stimulating novel photoreceptors-*e.g.*, melanopsin receptors in the retinal ganglion cells) and the use of psychotherapy and combination treatments to prevent future episodes of SAD rather than just treating the current episode. African-American patients may require either a modified protocol of light treatment or an early combination of different treatment modalities.

Applications

SAD could be quite disabling. Light treatment is safe and effective for SAD and appears attractive especially to patients concerned about the side effects of antidepressant medications, or who do not have time for psychotherapy. Furthermore, for patients who require combination with antidepressants, the dose of medication could be kept lower and thus minimize side effects at the end of Applications African-American SAD patients manifested a remission gap in comparison to Caucasian patients, and additional research will be needed to uncover what leads to it in order to design alternative treatment regiments to improve outcome.

Terminology

SAD refers to depressive episodes occurring during certain seasons and remitting spontaneously with change of season. The most common pattern is depression in fall/winter that remits in spring/summer.

Peer-review

The methodology is adequate and the manuscript is well written.

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SYSTEMATIC REVIEWS

Systematic review of evidence for different treatment settings in anorexia nervosa

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Abstract

AIM: To compare outcomes in anorexia nervosa (AN) in different treatment settings: inpatient, partial hospitalization and outpatient.

METHODS: Completed and published in the English language, randomized controlled trials comparing treatment in two or more settings or comparing different lengths of inpatient stay, were identified by database searches using terms "anorexia nervosa" and "treatment" dated to July 2014. Trials were assessed for risk of bias and quality according to the Cochrane handbook by two authors (Madden S and Hay P) Data were extracted on trial quality, participant features and setting, main outcomes and attrition.

RESULTS: Five studies were identified, two comparing inpatient treatment to outpatient treatment, one study comparing different lengths of inpatient treatment, one comparing inpatient treatment to day patient treatment and one comparing day patient treatment with outpatient treatment. There was no difference in treatment outcomes between the different treatment settings and different lengths of inpatient treatment. Both outpatient treatment and day patient treatment were significantly cheaper than inpatient treatment. Brief inpatient treatment followed by evidence based outpatient care was also cheaper than prolonged inpatient care for weight normalization also followed by evidence based outpatient care.

CONCLUSION: There is preliminary support for AN treatment in less restrictive settings but more research is needed to identify the optimum treatment setting for anorexia nervosa.

Key words: Anorexia nervosa; Treatment; Inpatient; Outpatient; Day patient

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Core tip: Anorexia nervosa (AN) is a serious disorder incurring high costs due to hospitalization. This study compared outcomes in AN treatment studies comparing different treatment settings: inpatient, day-patient and outpatient. Five studies were identified. There was no difference in outcomes between the different settings and lengths of inpatient treatment. Both outpatient and day-patient treatment were significantly cheaper than inpatient treatment. Brief inpatient treatment followed by evidence based outpatient care was cheaper than prolonged inpatient care for weight normalization. There is support for AN treatment in less restrictive settings but more research is needed to identify the optimum treatment setting.

Madden S, Hay P, Touyz S. Systematic review of evidence for different treatment settings in anorexia nervosa. *World J Psychiatr* 2015; 5(1): 147-153 Available from: URL: http://www.wjgnet.com/2220-3206/full/v5/i1/147.htm DOI: http://dx.doi.org/10.5498/wjp.v5.i1.147

INTRODUCTION

Anorexia nervosa (AN) is characterized by the restriction of energy intake relative to requirements leading to a significantly low weight for gender, age, developmental trajectory and height. Individuals with AN maintain an intense fear of gaining weight or becoming overweight even though they are underweight. They have a disturbance in the way in which they perceive their body weight and shape, there is undue influence of weight and shape on self evaluation and/or they deny the seriousness of their illness[1].

Lifetime prevalence rates for AN range from 0.9%-2.3% with its onset primarily in adolescence[2-5]. AN is the third most common chronic disorder affecting adolescent females, with and average mortality rate of 5%, up to 18 times greater than in non-affected women aged 15-24 years[6]. The course of the illness is often protracted with less than 50% of individuals with AN achieving full recovery in a period of seven years after the onset of their illness[7]. Physical complications include growth retardation, osteoporosis, infertility and changes in brain structure[8], while psychological complications include depression, anxiety disorders including obsessive compulsive disorder and cognitive impairment[9-11].

While the complications of AN have been well documented, there is limited evidence to guide as to what is the most appropriate treatment setting. Current expert consensus and guidelines[12,13] support outpatient care as the first line treatment in AN and there is a growing body of evidence to guide such care, particularly the role of family treatment in adolescents[14]. There are, however, few studies comparing different treatment settings in AN and few studies into the role of inpatient treatment in AN. Hospitalization of patients with AN for the management of acute medical instability (*e.g.*, hypothermia, hypotension, electrolyte abnormalities and cardiac arrhythmias) is thought to be essential in preventing mortality associated with AN[8,15], however, the benefits of inpatient weight restoration and the assumption that hospital is the best venue for refeeding once medical stability has been achieved remain unsupported by current evidence[16]. This problem is highlighted by a recent meta-analysis of 57 clinical trials in AN that found no difference in treatment effects based on the style of therapy or treatment setting[17].

Treatment settings for AN include inpatient, partial hospitalization (also known as day hospital care) and outpatient. Inpatient treatment programs are usually multidisciplinary and treatment focuses on weight restoration, normalizing eating behavior and facilitating psychological change through nutritional education, supervised meals and individual and group psychotherapy[18,19]. In published trials admissions have been prolonged with a length of stay ranging from several months to 15.2 wk[22-24]. Partial hospitalization or day programs are similar to inpatient treatment in terms of a multidisciplinary approach, treatments offered and intensity and duration of treatment but with no overnight stays[22]. They are potentially more flexible and thus amenable to matching the individual level of motivation for change with goals of treatment[24]. Outpatient treatment generally involves once or twice a week sessions with a therapist of a single discipline and may be either individual or family based[12,13,25]. Outpatient treatments provide care in the least restrictive setting and thus are favored by current psychiatric practice[12,13].

The present article aims to assess the effects of different treatment settings including inpatient, partial hospitalization and outpatient on treatment outcomes in AN and to assess the effects of continuing hospitalization for weight normalization compared with brief hospitalization for medical stabilization in AN. Primary outcome measures included measures of clinical improvement including weight as measured by body mass index (BMI) in adults or percentage expected body weight in children and adolescents (%EBW) and changes in eating disorder psychopathology.

MATERIALS AND METHODS

Literature search

For the purposes of the present review the authors (Madden S and Hay P) sourced trials identified in previous broad searches conducted for treatment guidelines for anorexia nervosa and other eating disorders[13,25]. The authors (Madden S and Hay P) then conducted a new database search dated Jan 2014 to July 21 2014 using (1) PubMed and (2) the Cochrane Central Register of Controlled Trials (CCRCT) Issue 6 of

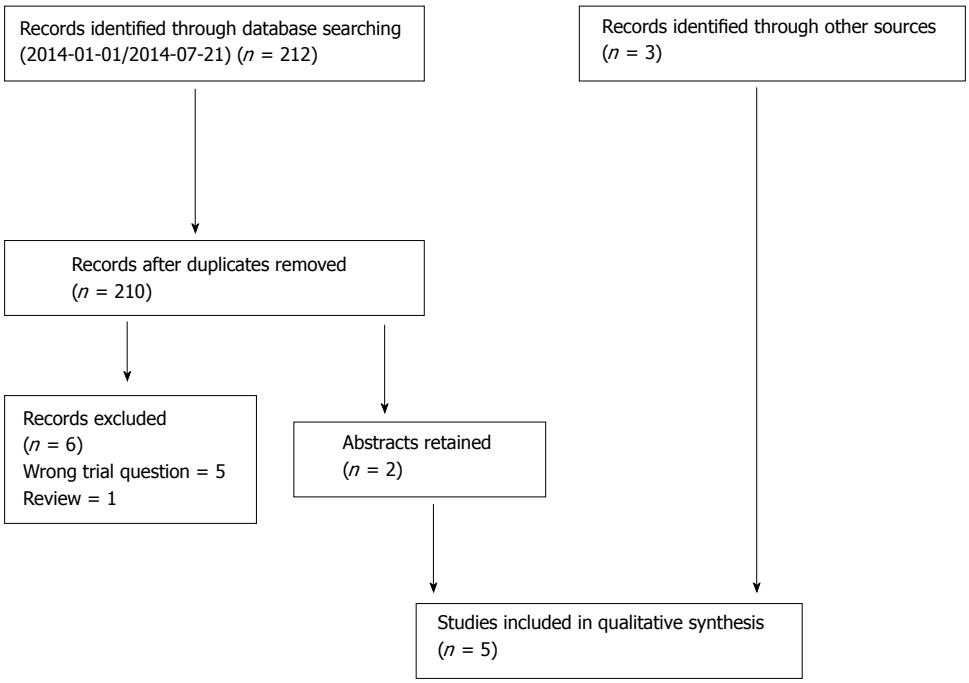

Figure 1 Flow diagram of literature search.

12, June 2014 using search terms "anorexia nervosa" and "treatment".

Trials were included if they were completed, published in English, reported a randomized comparison of different treatment settings or different lengths of inpatient treatment, were of participants meeting diagnostic criteria for AN and where the primary outcomes were an increase in weight and reduction in eating disorder psychopathology.

Trials were assessed for risk of bias and quality according to the Cochrane handbook[26] by two authors (Madden S and Hay P) Risk of bias was assessed on adequacy of randomization procedure and allocation concealment (*i.e.*, masking of group assignment), use of blinding in outcome assessments and data analysis applying an intention to treat analysis. Data were extracted on trial quality, participant features and setting, main outcomes and attrition.

Statistical analysis

The article is not a basic research or clinical research article and did not use biostatistics.

RESULTS

Results of search

Three trials[20,21,27] were sourced from the previous reviews[13,25]. The Pubmed search resulted in 192 titles for inspection and 7 abstracts for inspection of which 5 were not trials of treatment setting[28-32] and one was a review[33] and one new trial[34] was identified. The CCRCT Issue 6 of 12, June 2014 (*n* = 797723) search resulted in 20 titles for inspection of which two were duplicates and one new trial[29] was identified (Figure 1).

Of the five included studies, two compared inpatient treatment to outpatient treatment[20,21], one compared different lengths of inpatient treatment[29], one compared inpatient treatment to partial hospitalization[22] and one compared partial hospitalization with outpatient treatment[27]. These trials are presented in detail in Table 1.

Summary of findings

Of the two trials to compare inpatient treatment to outpatient treatment one included adult females[20] and one included male and female adolescents[21]. In both of these trials, participants in all of the active treatment arms showed significant improvements in weight and significant reductions in eating disorder psychopathology with the Crisp *et al*[20] trial demonstrating significantly better outcomes in both weight and eating disorder pathology, as measured by the Morgan-Russell scale, in the active treatment arms when compared with a single assessment. Additionally Gowers *et al*[35] reported improved treatment adherence and cost effectiveness with outpatient treatment, when compared to inpatient treatment, and higher parent satisfaction with specialist outpatient treatment. Patient satisfaction was reported to be highest with specialist treatment either in the inpatient or outpatient setting.

One trial compared different lengths of inpatient treatment, comparing brief hospitalization for medical stabilization with prolonged hospitalization for weight normalization[34]. In this trial there was no significant differences in outcome as measured by changes in weight and eating disorder pathology measured by Eating Disorder Examination[36]. Trial participants in the medical stabilization arm used significantly fewer total hospital days to 12 mo follow up than participants in

Table 1 Included randomised controlled trials evaluating the setting for treatment of anorexia nervosa

Ref.	Quality	Participants	Intervention	Outcome at end of treatment	Outcome at End of follow-up
Crisp *et al*[20],	Intention to treatment analysis, clear description of treatment and clear description of methodological problems High attrition rate, randomisation not described, lack of blinding, no power analysis and small numbers per group	90 adult female patients with DSM-IIIR AN with an illness duration of less than 10 yr. Specialist eating disorder service United Kingdom	Specialist, intensive inpatient treatment followed by 12 outpatient sessions 12 Outpatient individual and family psychotherapy including 4 sessions of dietary counselling 10 monthly outpatient group psychotherapy sessions (patient and parents) 4 sessions of dietary counselling Single assessment	Outcome took place 12 mo after the initial assessment regardless of when treatment finished All four groups increased weight significantly with weight gain in option 1 (9.6 kg), option 2 (9.0 kg), option 3 (10.1 kg) all being significantly higher than in option 4 (3.2 kg). All groups showed significant improvement in the Morgan-Russell scale. Groups 1 and 2 to $P < 0.01$ and groups 3 and 4 to $P < 0.05$ 2 All groups showed significant improvement in the Morgan-Russell scale. Groups 1 and 2 to $P < 0.01$ and groups 3 and 4 to $P < 0.05$	2 yr follow up Only available for Individual outpatient and single assessment groups. Participants who received individual outpatient treatment had significantly higher weight, BMI, and mean matched population weight changes than the assessment only group. The treatment group experienced significantly greater improvement in the socioeconomic adjustment subscale or the Morgan Russell scale but there was not significant difference in other subscales or the global score of the Morgan-Russell scale
Kong[27]	Apriori power analysis and low attrition rate. Unclear blinding and concealment of randomisation. Small numbers per group and no intention to treat analysis	50 adult female participants with DSM-IV eating disorder. AN (32%), BN (42%) and EDNOS (19%). Specialist eating disorder service South Korea	Day treatment program. Multidisciplinary 4 d a week program for 8 to 14 wk Outpatient treatment (IPT, CBT) for 4 to 24 mo	Eating behaviours (binging and purging) EDI-2; weight and BMI; psychological symptoms EDI-2: depression (BDI) and self esteem (RSES). DTP patients compared to controls showed significantly less psychological symptoms of eating disorders (EDI-2), significantly less binge eating and purging, significantly higher mood and self esteem and significantly greater weight gain in AN patients	No follow up reported
Gowers *et al*[21]	Adequate allocation concealment with blinded assessors, apriori power analysis and adequately powered as a superiority trial with intention to treat analysis. High attrition rate	167 male and female adolescents (12 to 18 yr) with DSM-IV AN. England	Multi-disciplinary inpatient care in child and adolescent psychiatric units. ED pecialized outpatient care including motivational interviewing, CBT and family counselling Generic outpatient psychiatry treatment	Morgan Russell average outcome scale, HONOSCA (health of the nation outcome scale for Children and Adolescents)- clinician reported, EDI-2, HONOSCA self report, Family assessment device (FAD), Mood and Feeling questionnaire, BMI and Weigh for height	1 and 2 yr follow-up No significant differences in outcomes between the three interventions. Outpatient treatment more cost effective with higher treatment adherence. Increased parental satisfaction with specialist eating disorder treatment
Herpertz-Dahlmann *et al*[22]	Adequate allocation concealment with blinded assessors, apriori power analysis and adequately powered as a non-inferiority trial with intention to treat analysis. Low attrition rate	172, female patients aged 11 to 18 years with DSM-IV AN with a BMI below the 10th centile and their first admission to hospital for AN. The setting was 5 university hospitals and one general hospital for general child and adolescent psychiatry in Germany	3 wk inpatient admission followed by day patient treatment based on weight restoration, nutritional counselling, CBT and family therapy until patients maintained their target weight for 2 wk 3 wk inpatient admission followed by inpatient treatment based on weight restoration, nutritional counselling, CBT and family therapy until patients maintained their target weight for 2 wk	Primary outcome was the difference in BMI between admission and follow-up. Secondary outcome measures included: Morgan-Russell Outcome Scores, EDI-2, Brief Symptom inventory total scores, eating disorder readmission and the difference in cost between the two programs No significant difference in primary outcome. Insurance costs 20% less in day treatment	12 mo follow-up. No significant differences in primary and secondary outcome measures. Insurance costs 20% less in day treatment
Madden *et al*[34]	Adequate allocation concealment with blinded assessors, apriori power analysis and adequately powered as a superiority Low attrition rate	82 participants aged 12 to 18 yr, medically unstable with DSM-IV AN of less than 3 yr duration	Brief inpatient tabilizationn for medical tabilization (MS) (av. 22 d) followed by 20 sessions of outpatient family based treatment (FBT) Inpatient hospitalisation for weight restoration (WR) to 90% expected body	Outcomes at the end of treatment included the percentage of patients at full and partial remission, the percentage EBW and EDE global scores There were no significant differences between groups	12 mo follow up. Primary outcome was the number of days of hospitalisation following the initial admission Secondary outcome was the total hospital days used to and the percentage of patients at full and partial remission. Other outcomes included the percentage

	weight (EBW) (38 d) followed by 20 sessions of outpatient manualised FBT	change in EDE global scores from baseline, readmission rates and the percentage of patients requiring treatment post protocol The only significant difference between groups was the total number of hospital days used which was significantly higher in the WR group

AN: Anorexia nervosa; FBT: Family based treatment; WR: Weight restoration; FAD: Family assessment device.

the weight restoration arm resulting in significant costs savings.

Partial hospitalization was compared to both inpatient treatment[22] and outpatient treatment[27]. When partial hospitalization was compared to inpatient treatment there was no difference in patient outcomes at either the end of treatment or at 12 mo follow up though treatment costs were reported to be 20% less in the partial hospitalization arm[22]. Partial hospitalization was, however reported to lead to significantly better outcomes compared to outpatient treatment with significantly less psychological symptoms, significantly less binge eating and purging, significantly higher weight gain and significantly higher mood and self-esteem[27].

DISCUSSION

Of the five trials only one demonstrated differences in treatment outcomes for AN in different treatment settings, notably better weight and psychological outcomes for those treated with partial hospitalization compared to outpatient treatment[27]. This trial, however, had a moderate risk of bias. While the trial had a low attrition rate, subject numbers were low (n = 50) and less than one third of the patients had AN (n = 14) with the remainder meeting diagnostic criteria for bulimia nervosa or eating disorder not otherwise specified. There was no intention to treat analysis and it was unclear if the outcome assessor carrying out the statistical analysis was blind to patient allocation.

None of the other four trials showed differences in treatment outcomes for AN in adults or adolescents based on treatment settings. The treatment studies did demonstrate reduced costs for shorter inpatient hospital admissions compared with longer inpatient hospitalization[34] and reduced costs for partial hospitalization[22] and outpatient treatment[35] compared to inpatient care. On the basis of treatment outcome it is not possible to recommend one treatment setting over another, however, based on the consistent finding of increased costs it is difficult to support the use of inpatient treatment in AN in the absence of medical instability or other risk issues and even in these circumstances difficult to support inpatient treatment beyond medical stabilization[15,17,34].

These four trials were of moderate to high quality with the risk of bias minimized through the use of intention to treat analysis in all of these trials and in the three most recent trials, adequate allocation concealment, blinded assessors and *apriori* power analysis[21,22,34]. The number of trials is, however, small and compares different aged populations including adults[20] and adolescents[21,22,34], different treatment setting comparisons with only the one trial comparing partial hospitalization with inpatient treatment being adequately powered as a non-inferiority trial[22].

Strengths of this present review included the use of two authors in the literature search and evaluation of articles and data extraction. The main limitations were the inclusion of English language and use of published papers only.

It is clear is that whilst all of these trials are supportive of treatment in less intensive and restrictive settings more research is needed comparing both different treatment settings and different lengths of inpatient stays before conclusive recommendations can be made regarding the optimum treatment setting in AN. This is particularly the case in adults with AN where studies have been of lower quality. It is also important that when new studies are planned that they are adequately powered as non-inferiority trials.

COMMENTS

Background

Anorexia nervosa (AN) is a serious disorder incurring high treatment costs, particularly due to hospitalization. While the complications of AN have been well documented, there is limited evidence to guide as to what is the most appropriate treatment setting. Current expert consensus and guidelines support outpatient care as the first line treatment in AN.

Research frontiers

Treatment settings for AN include inpatient, partial hospitalization and outpatient. Inpatient treatment programs are usually multidisciplinary and treatment focuses on weight restoration, normalizing eating behavior and facilitating psychological change. Partial hospitalization or day programs are similar to inpatient treatment but are potentially more flexible and thus amenable to matching the individual level of motivation for change. Outpatient treatments provide care in the least restrictive setting and thus are favored by current psychiatric practice. Current evidence including a recent meta-analysis of 57 clinical trials in AN that found no difference in treatment effects based on the style of therapy or treatment setting.

Innovations and breakthroughs

The present article aims to assess the effects of different treatment settings including inpatient, partial hospitalization and outpatient on treatment outcomes in AN and to assess the effects of continuing hospitalization for weight normalization compared with brief hospitalization for medical stabilization in AN using a systematic review. Five studies were identified, two comparing inpatient treatment to outpatient treatment, one study comparing different lengths of inpatient treatment, one comparing inpatient treatment to day patient treatment and one comparing day patient treatment with outpatient treatment.

Applications

The findings of this systematic review are supportive of the treatment of AN in less intensive and restrictive settings, though more research is needed comparing both different treatment settings and different lengths of inpatient stays before conclusive recommendations can be made regarding the optimum treatment setting in AN.

Terminology

Anorexia nervosa is characterized by the restriction of energy intake relative to requirements leading to a significantly low weight for gender, age, developmental trajectory and height. Individuals with AN maintain an intense fear of gaining weight or becoming overweight even though they are underweight. They have a disturbance in the way in which they perceive their body weight and shape, there is undue influence of weight and shape on self evaluation and/or they deny the seriousness of their illness.

Peer-review

This study compared the outcomes in anorexia nervosa in different treatment settings, and found a preliminary support for the treatment in less restrictive settings.

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SYSTEMATIC REVIEWS

Brain-derived neurotrophic factor levels in first episode of psychosis: A systematic review

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Abstract

AIM: To systematically review studies measuring peripheric brain-derived neurotrophic factor (BDNF) levels on first-episode psychosis patients and variables related to them.

METHODS: A systematic search was made of articles published in the Medline database from 2002 up to June 2014. Included are original studies that report enzyme-linked immunosorbent assay measurement of BDNF levels in serum or plasma in patients with a diagnosis of first episode psychosis (FEP) and age- and gender- matched healthy controls.

RESULTS: Of the initially identified 147 articles, only 18 satisfied the inclusion criteria. Of this, 15 found a significant reduction in patients with FEP compared with age- and gender - matched controls.

CONCLUSION: Peripheral BDNF levels are generally reduced in FEP patients. There are some factors that may influence BDNF levels that need to be further studied. Furthermore, a future meta-analysis in this topic is needed.

Key words: Brain-derived neurotrophic factor; Psychosis

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Core tip: Brain-derived neurotrophic factor (BDNF) has an important role during brain development and various studies have reported altered peripheral BDNF levels in schizophrenia, but findings are inconsistent. Some studies have been carried out specifically in first episode patients to address this issue. In the present study we have systematically reviewed studies measuring BDNF levels in first episode psychosis (FEP) patients compared to healthy controls and variables related to them. Most studies report reduced BDNF levels in FEP patients but some factors that may influence BDNF levels need to be further studied.

Toll A, Mané A. Brain-derived neurotrophic factor levels in first episode of psychosis: A systematic review. *World J Psychiatr* 2015; 5(1): 154-159 Available from: URL: http://www.wjg-

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INTRODUCTION

Brain-derived neurotrophic factor (BDNF) is the most widely distributed neurotrophin in the central nervous system and is highly expressed in the hippocampus and the prefrontal cortex (areas implicated in schizophrenia symptoms[1]. BDNF has an important role during brain development as it is implicated in many essential functions, including neurogenesis, neuronal differentiation, survival and normal maturation of neurodevelopmental pathways[2]. BDNF also has a significant role in the adult brain, regulating neuronal integrity, promoting synaptic plasticity, modulating synthesis, metabolism and release of neurotransmitters (dopamine, γ-aminobutyric acid, serotonin and glutamate), and moderating neuroplasticity processes[3].

As abnormalities in brain development and plasticity have been related to the pathophysiology of schizophrenia, there is a growing interest in understanding the role of BDNF in this disease. Interestingly, BDNF crosses the blood-brain barrier and serum concentrations strongly correlate with brain levels[4]. Low serum BDNF levels have been associated with decreased hippocampal volume, an area that has been strongly related to schizophrenia[5]. A meta-analysis conducted by Green *et al*[6] in 2011 indicated that BDNF levels were altered in patients with schizophrenia, with numerous studies, but not all, reporting reduced levels. They concluded that peripheral BDNF levels were moderately reduced in schizophrenia samples, including drug naïve and medicated patients, when compared with age-matched healthy controls. They also found an accelerated decrease with age, although they observed a high heterogeneity in BDNF levels between the different studies. Furthermore, their results could not support the greater decrease in men than in women that had previously been observed. The reasons for the heterogeneity in BDNF levels between different studies could be due in part by the fact that some patients were evaluated while on antipsychotic treatment. Atypical antipsychotics may increase, whereas treatment with conventional antipsychotics may decrease, peripheral BDNF levels[7]. Moreover, they did not take into account illness characteristics, such as illness stage. BDNF alterations throughout the course of illness are still unclear.

Identifying BDNF alterations in first episode psychosis (FEP) is a preliminary step to understanding the role of BDNF in schizophrenia pathophysiology, as first episode patients are not affected by medication effects (in some cases), or other factors related with chronicity[8]. Several studies have been carried out in FEP patients to identify peripheral BDNF alterations. Therefore, the aim of the present study was to systematically review these studies measuring peripheral BDNF levels in FEP (drug-naïve or medicated) patients and analyze the variables related with them.

MATERIALS AND METHODS

Search strategy

A systematic search was made of articles published in the Medline database using the following keywords: "schizophrenia", "psychosis", and "first episode" in combination with "bdnf", "serum", "plasma", and "peripheral". Articles in both English and Spanish published from 2002 up to June 2014 were selected. Indexed references in the retrieved articles that met the inclusion criteria were manually searched for additional relevant studies.

Inclusion/exclusion criteria

Included in the systematic review are original studies that report enzyme-linked immunosorbent assay measurement of BDNF levels in serum or plasma[6] in patients with a diagnosis of FEP and age- and gender-matched healthy controls. We excluded studies reporting data for patients with comorbid neurologic disorders or other psychiatric illnesses. We also excluded studies that reported peripheral BDNF levels in chronic schizophrenia patients and studies that only reported BDNF genetic data.

From the included studies, we assessed age and gender characteristics. We analyzed statistical differences in age and gender percentage between studies with lower BDNF levels than controls and those that did not with a *t*-test.

Statistical analysis

A statistical review has been performed by a biomedical statistician.

RESULTS

A diagram describing the selection of studies is presented in Figure 1. Of the initially identified 147 articles, only 18 satisfied the inclusion criteria[5,9-25]. Characteristics of these studies are described in Table 1. Seven articles reported BDNF levels in plasma and 11 studies reported levels in blood serum. Moreover, 13 articles reported BDNF levels only in drug-naïve patients and 5 studies reported BDNF levels in medicated patients (the most used antipsychotics were olanzapine, risperidone, quetiapine, aripiprazole and clozapine). When a study measured blood BDNF levels at two different time points, such as the studies that reported BDNF levels in schizophrenia patients before and after antipsychotic treatments, we included only data from the baseline without treatment. A detailed description of the results from the included studies is summarized in Table 2.

Of the 18 articles that measured BDNF levels at

Table 1 Characteristics of the included studies

Ref.	Sample	Age (yr)	Matched for	Illness duration (yr)	Medication	BDNF measurement
Jockers-Scherübl *et al*[9]	157 FEP 72 Ctl	31.8 32.3	Age, gender	Not reported	Drug naïve	Serum
Zakharyan *et al*[10]	25 FEP 105 Ctl	25.3 ± 9.2 37.3 ± 11.3	Age, gender	18.4 ± 7.2	Drug naïve	Plasma
Murphy *et al*[11]	15 FEP 15 Ctl	18.6 ± 3.3 18.5 ± 3.1	Age, gender	Not reported	Quetiapine	Serum
Sotiropoulou *et al*[12]	50 FEP 50 Ctl	29.84 ± 8.20 31.36 ± 7.96	Age, gender	Not reported	Drug naïve	Serum
Ruiz de Azua *et al*[13]	47 FEP 47 Ctl	24.3 ± 8.5 24.0 ± 8.8	Age, gender, education level	Not reported	Drug naïve, Rsp, Olz	Plasma
Yoshimura *et al*[14]	50 FEP 50 Ctl	30.8 ± 5.3 32.3 ± 7.1	Age, gender	Not reported	Apz	Plasma
Rizos *et al*[5]	20 FEP 21 Ctl	30.8 ± 10.5 34.0 ± 4.7	Age, gender, education level, employment	Not reported	Drug naïve	Serum
González-Pinto *et al*[15]	18 FEP 18 Ctl	24.39 ± 6.53 25.19 ± 5.95	Age, gender	Not reported	Drug naïve[1]	Plasma
Rizos *et al*[16]	37 FEP 22 Ctl	26.81 ± 9.22 26.59 ± 4.47	Age, gender	Not reported	Drug naïve	Serum
Jindal *et al*[17]	41 FEP 41 Ctl	22.40 ± 5.47 22.31 ± 5.67	Age, gender	Not reported	Drug naïve	Serum
Goto *et al*[18]	18 FEP 18 Ctl	29 ± 11 30 ± 11	Age, gender	9.4 ± 6.8	Drug naïve, Rsp/Olz/Apz	Serum
Pillai *et al*[19]	34 FEP 36 Ctl	32.19 ± 8.74 38.30 ± 1.26	Age, gender	Not reported	Drug naïve	Plasma
Rizos *et al*[20]	31 FEP 22 Ctl	26.81 ± 9.22 26.81 ± 9.22	Age, gender, education level, employment	Not reported	Drug naïve	Serum
Chen da *et al*[21]	88 FEP 90 Ctl	29.2 ± 9.6 29.8 ± 9.8	Age, gender, education level, smoking	23.4 ± 19.1	Drug naïve	Serum
Rizos *et al*[22]	14 FEP 15 Ctl	25.4 ± 5.8 26.6 ± 5.0	Age, gender, education level, employment	Not reported	Drug naïve	Serum
Buckley *et al*[23]	15 FEP 14 Ctl	21.00 ± 8.83 25.00 ± 5.72	Age, gender	25.2 ± 33.0	Drug naïve	Plasma
Palomino *et al*[24]	48 FEP 43 Ctl	23.7 ± 1.0 25.5 ± 0.8	Age, gender	Not reported	Atypical, mood stabilizers	Plasma
Pirildar *et al*[25]	22 FEP 22 Ctl	27.81 ± 9.54 25.7 ± 5.8	Age, gender	15.2 ± 13.0	Drug naïve[1]	Serum

[1]BDNF levels were also assessed after antipsychotic treatment (Olz, Rsp, Cloz) but not included in the review. Data are presented as mean ± SD. Apz: Aripiprazole; BDNF: Brain-derived neurotrophic factor; Cloz: Clozapine; Ctl: Controls; FEP: First episode psychosis; Olz: Olanzapine; Rsp: risperidone.

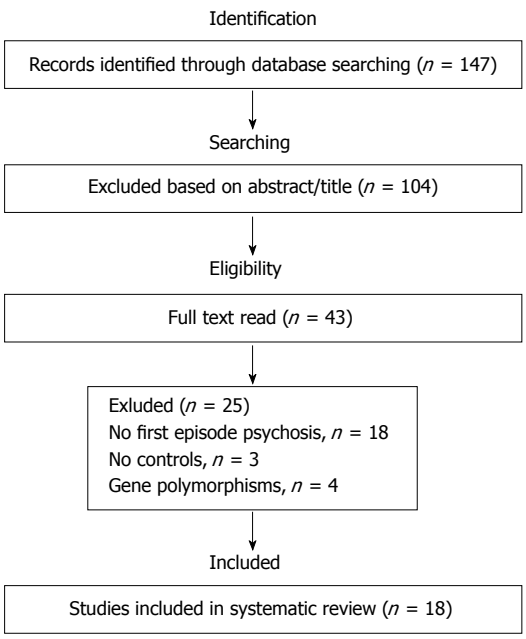

Figure 1 Flow diagram describing the selection of studies.

baseline, 15 found a significant reduction in patients with FEP compared with age- and gender-matched controls.

There were no statistical differences in mean age between those studies that found lower BDNF levels in patients than those that did not (26.18 ± 3.89 *vs* 29.11 ± 3.50, P = 0.24) The percentage of men was lower in the studies that found decreased BDNF levels in patients compared to those that did not (47.89% *vs* 54.71%, P = 0.36).

DISCUSSION

We found 15 out of 18 articles found a reduction in BDNF levels compared to age- and gender-matched controls. It is important to note that 13/18 studies included only drug-naïve patients and 2 included drug-naïve and medicated patients. Televe out of 15 studies that found a decrease were conducted in drug-naïve patients whereas two of the three studies that found no alteration in BDNF included medicated patients.

Table 2 Basal levels of brain-derived neurotrophic factor

Ref.	FEP (ng/mL)	Controls (ng/mL)	Results	Effect size d (CI)
Jockers-Scherübl *et al*[9]	13.1 ± 5.9	13.2 ± 0.2	No difference	0.10 (-0.18-0.38)
Zakharyan *et al*[10]	0.176 ± 0.014	0.24 ± 0.3	↓ in FEP	1.21 (0.75-1.67)
Murphy *et al*[11]	Missing data	Missing data	No difference	-
Sotiropoulou *et al*[12]	12620 ± 1860	14520 ± 2180	↓ in FEP	0.64 (0.23-1.04)
Ruiz de Azua *et al*[13]	6.09 ± 3.70	9.19 ± 4.21	↓ in FEP	0.66 (0.24-1.07)
Yoshimura *et al*[14]	0.7 ± 0.4	Missing data	↓ in FEP	0.43 (0.03-0.82)
Rizos *et al*[5]	9.76 ± 4.61	15.33 ± 6.34	↓ in FEP	0.99 (0.34-1.64)
González-Pinto *et al*[15]	4.09 ± 2.31	5.80 ± 2.66	↓ in FEP	-
Rizos *et al*[16]	18.87 ± 8.23	29.20 ± 7.73	↓ in FEP	0.72 (0.17-1.26)
Jindal *et al*[17]	0.09 ± 0.03	0.117 ± 0.04	↓ in FEP	0.54 (0.10-0.99)
Goto *et al*[18]	Missing data	Missing data	No difference	0.38 (-0.28-1.04)
Pillai *et al*[19]	Missing data	Missing data	↓ in FEP	0.53 (0.05-1.00)
Rizos *et al*[20]	Missing data	Missing data	↓ in FEP	-
Chen da *et al*[21]	9.0 ± 4.2	12.1 ± 2.2	↓ in FEP	0.92 (0.61-1.23)
Rizos *et al*[22]	23.90 ± 5.99	30.00 ± 8.43	↓ in FEP	0.83 (0.07-1.59)
Buckley *et al*[23]	0.017 ± 0.003	0.049 ± 0.007	↓ in FEP	1.37 (0.56-2.18)
Palomino *et al*[24]	4.19 ± 2.26	7.55 ± 4.31	↓ in FEP	0.56 (0.13-0.97)
Pirildar *et al*[25]	14.2 ± 8.1	26.8 ± 9.3	↓ in FEP	1.07 (0.93-1.7)

Data are presented as mean ± SD. FEP: First episode psychosis.

These results are consistent with some studies pointing out normalization in BDNF levels with treatment. However, other additional factors may influence BDNF alterations.

Another factor that could affect BDNF levels is the mean age of patients, as a greater reduction in peripheral BDNF in schizophrenia was reported with increasing age in Green *et al*[6]. We did not find statistical differences in mean age between those studies that found lower BDNF levels in patients than those that did not. However we must take into account that our age variance was much smaller than in Green *et al*[6] study.

On the other hand, although some articles have described a greater reduction in BDNF in males than females with schizophrenia[6], this does not appear to be a factor in the present analysis, even after taking into account the size effect (results upon demand). This results are in agreement with Green *et al*[6] who found no a reduction in both men and women in BDNF after excluding an outlier.

Patients clinical characteristics, could also affect BDNF levels. It would be interesting to conduct a prospective study on high risk psychosis patients through different illness stages to clarify this issue.

Another important variable to consider is substance use, particularly cannabis use. Cannabis use is very common in first episode patients, with a prevalence ranging from 30% to 60%[26]. Moreover, in non-psychotic patients, it has been described that acute cannabis use can initially increase, whereas chronic use can decrease, peripheral BDNF levels[27]. However, cannabis use was an exclusion criterion in most studies, but not in all. Specifically, the article by Jockers-Scherübl *at al*[9] compared BDNF levels between FEP patients and controls that used and did not use cannabis[9]. They found increased BDNF levels in FEP cannabis-users than non-users and controls. These results are in disagreement with a more recent study[27]. Further research should therefore be performed to clarify the effects of cannabis use on BDNF levels in FEP patients. The effect of the val66met BDNF polymorphism and the interaction between this polymorphism and cannabis use could also affect BDNF levels. A Val to Met substitution at codon 66 of the BDNF gene, is known to result in less efficient intracellular trafficking and decreased activity-dependent BDNF secretion and has been related to psychosis emergence[28]. Furthermore a study has described an interaction effect between cannabis, this polymorphism and gender, on the risk of psychosis emergence[29].

Other environment factor should also affect BDNF levels. A history of childhood trauma has been related to a reduction of BDNF levels[30].

Limitations

A limitation of this type of systematic review is that some relevant studies, including those that are unpublished, may be overlooked. Another limitation is the marked heterogeneity of the articles included in the review in relation to the sample size, the mean age of the patients, the proportion of men/women, the illness duration (only reported in six studies), the medication type (in patients receiving treatment), and the type of symptomatology patients were presenting. Furthermore, we did not take into account the effect of the BDNF polymorphism, and it could have multiplicative on lower BDNF levels.

Peripheral BDNF levels are generally reduced in FEP patients. However, there are some factors that may influence BDNF levels that need to be further studied, which will help to resolve inconsistencies in the literature. Furthermore, a future meta-analysis on

this topic would help to clarify BDNF alterations in FEP.

COMMENTS

Background

Altered brain-derived neurotrophic factor (BDNF) levels have been described in schizophrenia, and have been related to brain abnormalities, but findings are still inconsistent. Moreover, BDNF alterations throughout the illness course are still unclear.

Research frontiers

Neuroimaging in schizophrenia; neurodevelopment in schizophrenia; neuroplasticity in schizophrenia; neurodegeneration in schizophrenia.

Innovations and breakthroughs

This is the first work that systematically reviews studies measuring peripheric BDNF levels in first episode patients, a group of patients not affected by cronicity.

Applications

Comprehending BDNF alterations in first episode patients is a preliminary step to understanding the role of BDNF in schizophrenia pathophysiology and brain structure alterations.

Terminology

Neurotrophic factors are a family of proteins that are responsible for the growth and survival of developing neurons and the maintenance of mature neurons.

Peer-review

This is an interesting manuscript.

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